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Front cover illustration by Brett Clayton
Division of Biomedical Communications,
Department of Surgery, University of Toronto.

Editorial

Welcomc to thc first issuc of thc *UTMJ* for the 1998-99 publication year!

Volume 76, numbcr 1, begins with threc original articles which rcflcct the *UTMJ's* commitment to publish matcrial that reflect scicntific, clinical, and psychosocial fields within medicinc. Our original articlcs are pcer-reviewcd by an cditorial board composcd of staff and medical studcnts. This issuc starts with a review of the basic science and inflammatory proccssc̄s behind cystic fibrosis, followed by an assessment of the rolc of fiber in thc management of irritablc bowcl syndrome. Finally, you will find an in-depth look at the ethics of relocating physicians to underserviced areas.

The 1998-99 *UTMJ* includcs many of the popular scctions with which our rcadcrs are familiar. Ncws and Views provides a look at items of intcrcst in thc current medical literaturc, along with analysis and coverage of events and issucs that concern thc mcdical profcssion. In this issue, News and Views is pleased to bc launching a three part scries on Complimcntary and Alternative Medicine. We also are proud to present our superb clinical scctions: Clinicopathological Correlation, Quick Diagnosis, and Morning Report. Prepared in conjunction with staff in the Toronto tcaching hospital community, these scctions will test the clinical acumen of both studcnts, resident,s and scasoned physicians. Finally, the Technology and Book Reviews sections keep our rcadcrship up to datc by reviewing recent software, internct tools, and books relatcd to health scicncc̄s and clinical mcdicine.

The 1998-99 *UTMJ* wclcomes back expert illustrations from thc Biomedical Communications studcnts at Thc University of Toronto. These illustrations grace thc *UTMJ's* cover and add impact to our articles. In addition, we invite readcrs to visit our wcbsite to browse back issues: http://dantc.med.utoronto.ca/UTMJ.

Last ycar, the *UTMJ* marked its 75th anniversary with a new look and expanded format. For its 76th year of publication, the staff of the 1998-99 UTMJ is committed to producing the high quality publication that thc readcrship of thc journal has come to expcct. We encouragc fcedback to thc *UTMJ* in the form of letters and cditorials rcgarding anything we publish.

Please direct to the Editors, (sandra.demarics@utoronto.ca or g.thanassoulis@utoronto.ca).

Enjoy!

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The editors apologize for any omissions to the above list; this list represents our final version at press time. We will update the list in future issues.

Letter to the Editors

We are writing to comment on the article by Cohen (On the Health Benefits of Alcohol), which appeared in the March 1998 issue of the *UTMJ*.

As Cohen pointed out, the evidence that alcohol consumption offers protection against coronary artery disease is now substantial. However, two additional points must be emphasized with regards to this protection. First, most of the protection is conferred by drinking small amounts of alcohol – as little as one drink every other day.[1] Second, the coronary heart disease benefit conferred by alcohol consumption has been demonstrated only in middle aged and older persons, among whom coronary heart disease is the leading cause of death. Among younger persons alcohol-related accidents, violence, and injuries are a major concern with regard to morbidity and mortality, and the risks of these outcomes increase directly with increasing alcohol consumption.[2]

In the fall of 1997, new Low Risk Drinking Guidelines for Canadians were released by the Addiction Research Foundation and the Canadian Centre on Substance Abuse.[3] These guidelines take into account the benefits, as well as the risks of alcohol consumption. In so doing, they consider both the acute and long-term effects of drinking alcohol. Core recommendations in these guidelines are that men and women should not drink more than two drinks per day and that weekly consumption should not exceed nine drinks for women and fourteen drinks for men. These recommendations are based on a critical assessment of the evidence from epidemiological studies concerning an array of health outcomes, complemented by clinical and laboratory findings.

Canadian physicians can play two key roles in counseling patients with regard to alcohol use. First, they can reinforce the appropriateness of the low risk drinking pattern that most of their patients will manifest. The new guidelines provide the basis for such reinforcement. Second, they can encourage and assist patients who are drinking in patterns that are not low risk to modify their drinking. To this end, the College of Family Physicians of Canada has developed the Alcohol Risk Assessment and Intervention (ARAI) program.[4]

Yours sincerely,

Mary Jane Ashley MD, FRCPC, Professor
Susan Bondy PhD, Assistant Professor
Jurgen Rehm PhD, Professor

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Inflammation in the Cystic Fibrosis Lung

Peter K. Stotland, MSc. (MD/Ph.D1), Danuta Radzioch, Ph.D,*
and Mary M. Stevenson, Ph.D**

Abstract

The major cause of morbidity and mortality among cystic fibrosis (CF) patients is chronic and recurrent lung infection with *Pseudomonas aeruginosa* (PA). The pathology in the airways is based on local inflammation and immune response(s) leading to inadequate clearance of bacteria and progressive damage to the structural and functional integrity of the lungs. It is widely recognized that an exaggerated inflammatory process in response to PA infection is the hallmark of lung disease in CF patients. This review article addresses key concepts needed to appreciate the complexity of CF lung disease.

Introduction

CF was identified in 1936 by Fanconi and further characterized 2 years later by Andersen.[1] Today it is recognized as the most common, lethal, autosomal recessive disorder affecting Caucasian populations[2-4] wherein the incidence is approximately 1 in 2,500 live births.[5,6] CF has a significant impact within Canada; in the Saguenay Lac-St. Jean region of Quebec the incidence can be as great as 1 in 891 live births.[7,8]

Thick, mucous, secretions associated with abnormal sweat chloride, pulmonary disease, and pancreatic disease characterize CF. Within affected airways, recurrent infection by opportunistic bacteria leads to lung disease and eventual res-

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piratory failurc. Other mainfestations of disease include male infertility, malabsorption of gut contents due to pancreatic insufficiency, and intestinal blockage (meconium ilcus).[9] In most cases, the diagnosis of CF is considered when one or more features (shown in Table 1) are present and then confirmed by a finding of more than 60 mmol/L chloride in the sweat.[10]

Table 1
Phenotypic Features Consistent with Diagnosis of CF

Chronic Sinopulmonary Disease
- Persistent colonization/infection with typical CF pathogens, including: *S. aureus*, non-typeable *H. influenza*e, mucoid and non-mucoid *P. aeruginosa*
- Chronic cough and sputum production
- Persistent chest radiograph abnormalities (i.e., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Airway obstruction manifested by wheezing and trapping
- Nasal polyps; radiographic or computed tomography abnormalities of paranasal sinuses
- Digital clubbing

Gastrointestinal and Nutritional Abnormalities
- Intestinal: exocrine pancreatic dysfunction; distal intestinal obstruction syndrome; rectal prolapse
- Pancreatic: pancreatic insufficiency; recurrent pancreatitis
- Hepatic: chronic hepatic disease manifested by clinical or histological evidence of focal billiary cirrhosis or multilobular cirrhosis
- Nutritional: failure to thrive (protein-calorie malnutrition); hypoproteinaemia and oedema; complications secondary to fat-soluble vitamin deficiency

Salt Loss Syndromes
- Acute salt depletion
- Chronic metabolic alkalosis

Male Urogenital Abnormalities
- Obstructive azoospermia

Adapted from Rosenstein and Zeitlin (1998)

By the early 1980's, the physiologic abnormalities in maintaining homeostatic ion transport across epithelial-lined organs in CF patients was attributed to the failure of cAMP regulated chloride transport.[11,12] In 1989, the CF gene, named *CFTR*, was identified[13-15] by both linkage analysis[16-18] and chromosome walking.[19] The CF gene was determined to reside in the region of chromosome 7q31.1 encompassing about 250 kb of genomic DNA and consisting of 27 exons. Expression of the 6.5 kb *CFTR* mRNA has been detected in the pancreas, nasal polyp, lung, colon, sweat gland, and liver tissues and encodes for a protein of 1480 amino acids, known as the cystic fibrosis transmembrane conductance regulator (*CFTR*).

A correlation between CF genotype and the severity of lung disease has yet to be established. CF patients carrying the same *CFTR* mutations display a remarkable heterogeneity in the severity of lung diseasc,[20,21] thereby suggesting the presence of modifier genes exclusive of the *CFTR* locus[22,23] and/or environmental factors.[2] These putative modifier gene(s) may be responsible for initiating or modulating the host response to PA airway colonization. Accordingly there is considerable interest among CF researchers to elucidate the proposed existence and/or function of these genes.

CFTR: Link to PA Lung Disease?

The link between mutations at the *CFTR* locus and bronchopulmonary infection with PA remains unresolved. A number of models have been established and are described below.

The traditional model proposes that CF patients have impaired cAMP mediated *CFTR* chloride secretion across the epithelial membrane of the respiratory tract. This model suggests that epithelial ion transport may be necessary for effective mucocilliary clearance by regulating both the volume and ionic composition of the airway surfacc fluid. Thus, with airway surface fluid concentrations of Cl^- being lower, increased absorption of Na^+ occurs, which in turn causes desiccation of mucus as water follows Na^+ across the epithelium. The net result of this altered ion transport is a reduced depth of airway surface fluid, impeded cilial action, and a viscous environment that predisposes airways to infcction.[24] According to this model, desiccated secretions may lead to trapping of bacteria in the lung and concomitant reduction in mucociliary clearance, which may allow bacterial infections to become established.[2]

Recently, studies have shown that excessive salt concentrations may be apparent in the airways of CF patients.[25-29] Results from these studies havc led to an alternate model that proposes airway epithelia regulate the ionic composition but not the volume of the airway surfacc fluid. Therefore, in CF, the airway epithelium would appear to have a reduced ability to reabsorb salt, similar to that of the sweat duct observed in CF patients. This excessive salt concentration is proposed to have a deleterious effect on the biological activity of a class of anti-microbial agents known as ß-defensins.[28-29]

There are conflicting reports as to whether the salt concentrations in airway surface fluid of CF patients is indeed altered. Recently, one group reported no detectable differences in the airway surface fluid osmolarity between CF patients and normal counterparts.[24] This indicates that further study is required to clarify the ionic composition of the airways surfacc fluid and its role in CF pathogenesis.

In addition to regulating ion transport, it has been suggested that the *CFTR* can also regulate the expression of sur-

face molecules on epithelial cells. It has been reported that asialoGM1 was expressed on 12% of nasal polyp epithelial cells recovered from CF patients whereas its expression was detected on only 2.9% of cells from normal patients.[31] Thus, the increased expression of surface molecules, such as asialoGM1, could mediate increased PA attachment.[32] These results form the basis of the proposed mechanism implicating PA pili as the key player in binding.[33]

Another possible explanation for susceptibility to PA lung infection concerns the expression of *CFTR* in the epithelial cells from the CF lung. Pier *et al.* (1996) hypothesized that the binding and internalization of respiratory pathogens by epithelial cells followed by desquamation could be an important mechanism for clearing bacteria from the airways. In support of this hypothesis, these investigators observed that cultured human airway epithelial cells expressing *CFTR* with the ΔF508 mutation were defective in the uptake of PA compared to cells expressing wild-type *CFTR*. From this it was concluded that *CFTR* itself was a factor contributing to host defense against PA. Moreover, they identified that LPS-core oligosaccharide is a bacterial ligand that binds to *CFTR*.[34] Subsequent experiments from the same group elucidated that *CFTR* is a cellular receptor that is responsible for the binding, endocytosis, and clearance of PA from the normal lung.[35]

CF Lung Disease: Initial PA Infection and Acute Inflammation

Although the connection between the genetic defect and PA colonization remains unresolved, chronic pulmonary disease ensues and its relentless course is the major cause of the morbidity and mortality associated with CF. Much effort has been directed to understanding why CF patients develop chronic PA lung infection and why their seemingly uncompromised immune systems are largely ineffective against this bacterium.

Respiratory viral infections, such as those caused by respiratory syncytial virus, have been hypothesized as initial triggering events leading to PA lung infection in CF patients.[36-38] Virus replication and subsequent host responses cause damage to the respiratory mucosa, thereby, facilitating bacterial adherence.[39] It is thought that the initial episodes of bacterial infection in the lower respiratory tract may occur with organisms such as *Staphylococcus aureus* and *Hemophilus influenzae* during infancy.[3,9,40] Following *Staphylococcus aureus* binding to fibronectin, an inflammatory response is evoked. As infection proceeds and becomes established, clearance of these organisms becomes increasingly ineffective due to the mucous production within the airways coupled with the effects of an intense inflammatory response predominated by PMN (polymorphonucleocytes). Infiltrating PMN release an array of oxidants, phagocytic enzymes, cytokines, and chemokines that have deleterious effects on delicate lung tissue[43] (Table 2). The infiltrating cells have substantial harmful effects to lung tissue, namely, by their ability to release elastase[39, 50-52] and by the increased amount of DNA released from dying PMN.[53, 54] Released elastase is capable of cleaving receptors on the surface of human T cells[55] and destroying key opsonins such as IgG,[41, 56] and complement receptors such as CR1.[51] As well, elastase stimulates the release of neutrophil chemoattractants,[57] promotes hypertrophy and hyperplasia of the mucus-secreting apparatus[58] and has marked proteolytic activity on fibronectin, which contributes to the pathology.[39-42] Damage caused to fibronectin by both the bacteria and host response exposes binding sites on the surface of epithelial cells, thus, facilitating the adherence of PA.[44]

Table 2
Major Products Released by PMN

Cytokines/ Chemokines	Proteins
• IL-1ß	• Fibronectin
• IL-1ra	• Heat shock proteins
• IL-8	• CR1
• TNF-α	• CR3
• TGF-ß	• FcR
• MIP-1α	• Lactoferrin
• IL-3	• Defensins
• GM-CSF	
• IFN-α	**Enzymes**
	• Elastase: serine and metalloenzyme
Biologically Active Lipids	• Acid hydrolases
• Platelet-activating factor (PAF)	• Myeloperoxidase
• Leukotriene B_4 (LTB_4)	• Lysozyme
• Prostaglandin E_2 (PGE_2)	• Neutral serine proteases
	• Plasminogen activator
Oxygen Metabolites	• Collagenase
• O_2, H_2O_2, OH	• Gelatinase
	• Heparanase

Adapted from Sibille and Reynolds (1990)

Thus, it appears that recurrent infections subsequent to initial triggering events occur and establish a microenvironment that predisposes the airways to chronic PA colonization by mediating further injury to the respiratory mucosa.[45] It remains unclear whether infection is required to incite a host inflammatory response or if inflammation precedes infection, thus, causing damage to the airways and, thereby, increasing the susceptibility of the lung to subsequent infection.[46-47] In order to investigate the latter possibility, Khan *et al.* (1995) characterized the inflammatory state of the airways of infants with CF. They determined that infants as young as 4 weeks of age, with no observable infection (either bacterial, viral or fungal), had a significantly heightened inflammatory response as reflected by elevated num-

bers of PMN, and elevated levels of elastase/alpha$_1$-antiprotease inhibitor complexes and IL-8 in their bronchoalveolar lavage fluid.[40] Furthermore, these observations support the hypothesis that there are indeed genes exclusive of the *CFTR* that modulate host responses in CF.

Regardless of the sequence of initiating events early in life, the ensuing host responses are insufficient to stop the inevitable course of persistent and recurrent PA infection and the resulting extensive tissue damage.[48-49]

CF Lung Disease: Chronic Inflammation

Despite the fact that the acute inflammatory response may serve as a first line of defense in some bacterial infections, this response fails to control PA infection in the CF lung. At some point between the initial infection and inflammation, or shortly thereafter, PA acquires a mucoid phenotype.[39, 45] A considerable production of alginate, an extracellular polysaccharide, forms a biofilm around the bacteria, thereby, encapsulating microcolonies of PA in the lungs.[59] Bacteria are protected against the host's defense mechanisms by the production of alginate and the concomitant aggregation into microcolonies.[60] As well, the release of toxins and proteases from PA may be important in preventing the host from mounting a protective local immune response.[38] The development of the mucoid phenotype may be an important factor in shifting from acute to chronic inflammation within the CF lung.

The mucoid biofilm not only impedes opsonising antibody, PMN and macrophage phagocytosis, but also contributes to further activation of inflammatory cells and antigen presentation cells.[61] This leads to continuous induction of inflammatory processes with persistent cellular recruitment to sites of infection.[42]

Attempts have been made to characterize the sustained inflammatory state of the CF lung by analysis of fluids obtained by both nasal and bronchoalveolar lavage (Figure 1). It is clear that a severe local inflammatory response is present in CF patients with mild lung disease who do not regularly produce sputum.[62] Bronchoalveolar lavage fluid

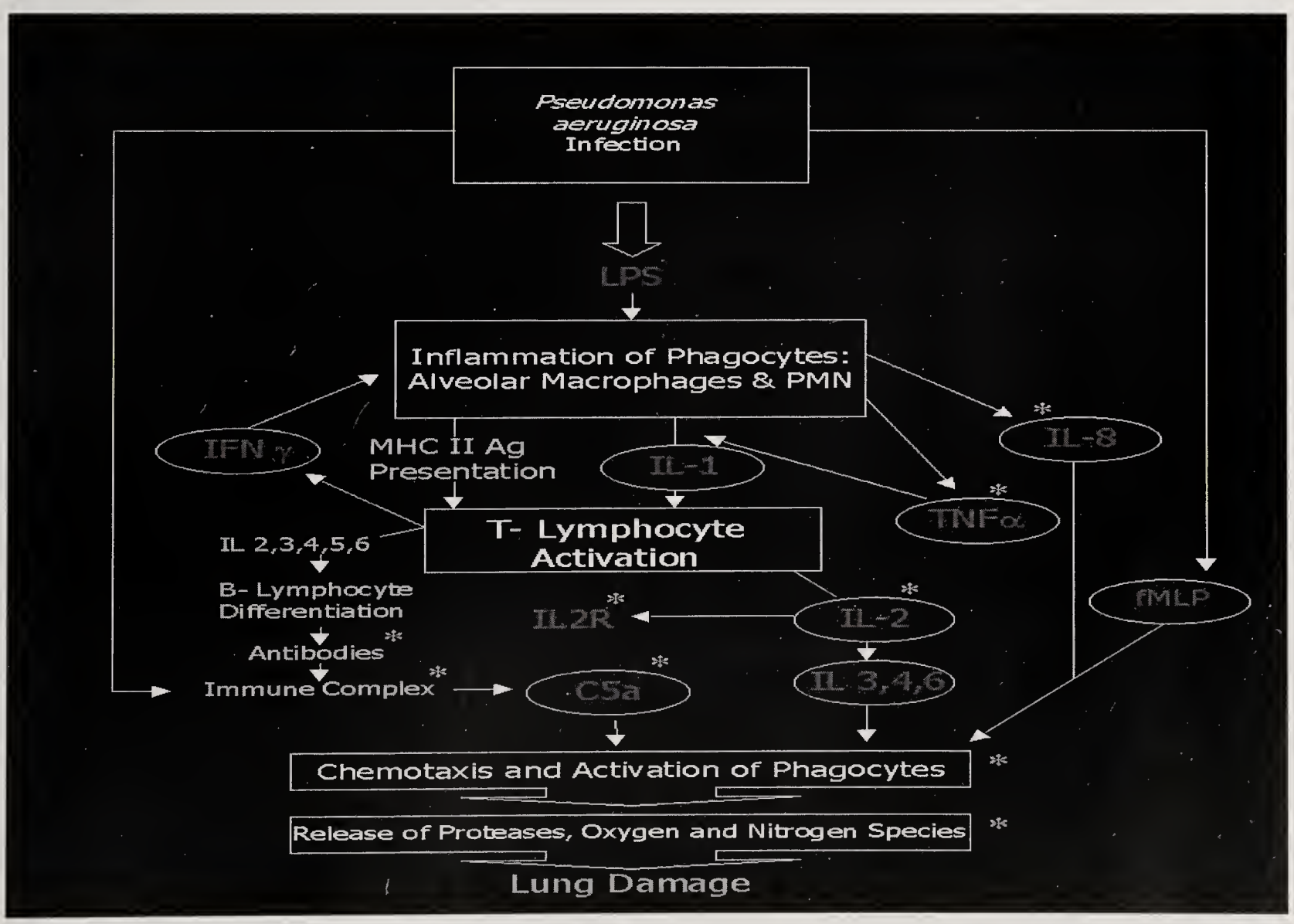

Figure 1. *Host response to bronchopulmonary Pseudomonas aeruginosa infection. * indicates areas of response which may be greatly exacerbated in CF. (Adapted from Berger, 1991 and Warner, 1991).*

obtained from the airways of CF patients with chronic lung disease have significantly higher numbers of PMN[42,48-49,62-64] and increased concentrations of elastase[52, 62] as compared to healthy control subjects. High levels of IL-8[65-67] and leukotriene B_4 (LTB_4)[68] have been reported to play an important role in mediating PMN recruitment to the lungs. Richman-Eisenstat *et al.* (1993) demonstrated that treatment with a monoclonal antibody against the PMN chemokine, IL-8, significantly inhibited the chemotactic activity in CF patients' sputum, but not in induced sputum recovered from healthy subjects.[69-70] Various sources of IL-8 in the CF lung have been reported and include epithelial cells,[71] alveolar macrophages[40, 66] and PMN themselves.[72-73]

Other cytokines have been implicated in progression of inflammation during PA infection. Significantly elevated levels of IL-1,[64, 74] IL-1ß,[64] and TNF-α[74-75] have been found within the bronchoalveolar lavage fluid of CF patients. In addition, IL-6 has been reported to be modestly elevated in infected CF patients compared with healthy control subjects.[65, 74] It has also been reported that bronchoalveolar lavage fluid from CF patients contained significantly less of the anti-inflammatory cytokine, IL-10, than did that of healthy control subjects.[74] In a subsequent study by the same group, it was determined that bronchial epithelial cells from healthy airways are capable of producing IL-10 and this production is defective in chronically infected CF lungs.[71] Therefore, the bronchial epithelium may play an important role in regulating the local immune response in airways through the production of IL-10, which in turn may suppress macrophage activity, antigen presentation and neutrophil phagocytosis.[77] CD4+ T cells from CF patients have also been shown to secrete significantly less IL-10 upon polyclonal activation in comparison to similarly treated cells obtained from healthy control patients.[78] Given that high levels of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α) and low levels of anti-inflammatory IL-10 are observed in the lungs of CF patients, it becomes apparent that IL-10 may play a key role in modulating the inflammatory responses to PA (Melvin Berger, personal communication).

Taken together, the observations made from bronchoalveolar lavage fluid studies suggest that airway damage likely results from the sum of acute and chronic infection and inflammation.[62, 76] These inflammatory processes are usually regulated such that a fine balance between pro- and anti-inflammatory cytokines is achieved in the airways. In CF, it appears that there may be an imbalance in these cytokines which predisposes to the increased inflammation in the airways.

Summary

Although the identity of the gene responsible for CF has been known for almost ten years, the definitive link between genetic defect, alteration in airway surface fluid ionic composition, and inflammation ensuing from PA lung infection remains to be determined. It is known that defects in the *CFTR* alter the salt concentrations in the airway surface fluid of CF patients but it is not clear what role this plays in PA infection. In addition, CF patients suffer from a severe and sustained lung inflammatory response characterized by high numbers of infiltrating cells, high levels of elastase release, and an apparent imbalance of pro- versus anti-inflammatory cytokines. Inflammation is not capable of eradicating PA from the CF lung, but rather leads to progressive loss of lung function. Indeed, the sequence of events leading to the development of chronic bronchopulmonary PA infection poses many questions, namely: Is inflammation definitively apparent before initial PA infection or does inflammation occur as a consequence of infection? Is it possible that *CFTR* plays a direct role in the dramatic inflammatory response to PA infection? Answers to these and other questions may offer new insights into the relationship between mutations of the *CFTR* and the inflammatory processes in the lung that lead to the observed pathology in CF patients.

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Should Dietary Fibre be Used in the Treatment of Irritable Bowel Syndrome? An Update

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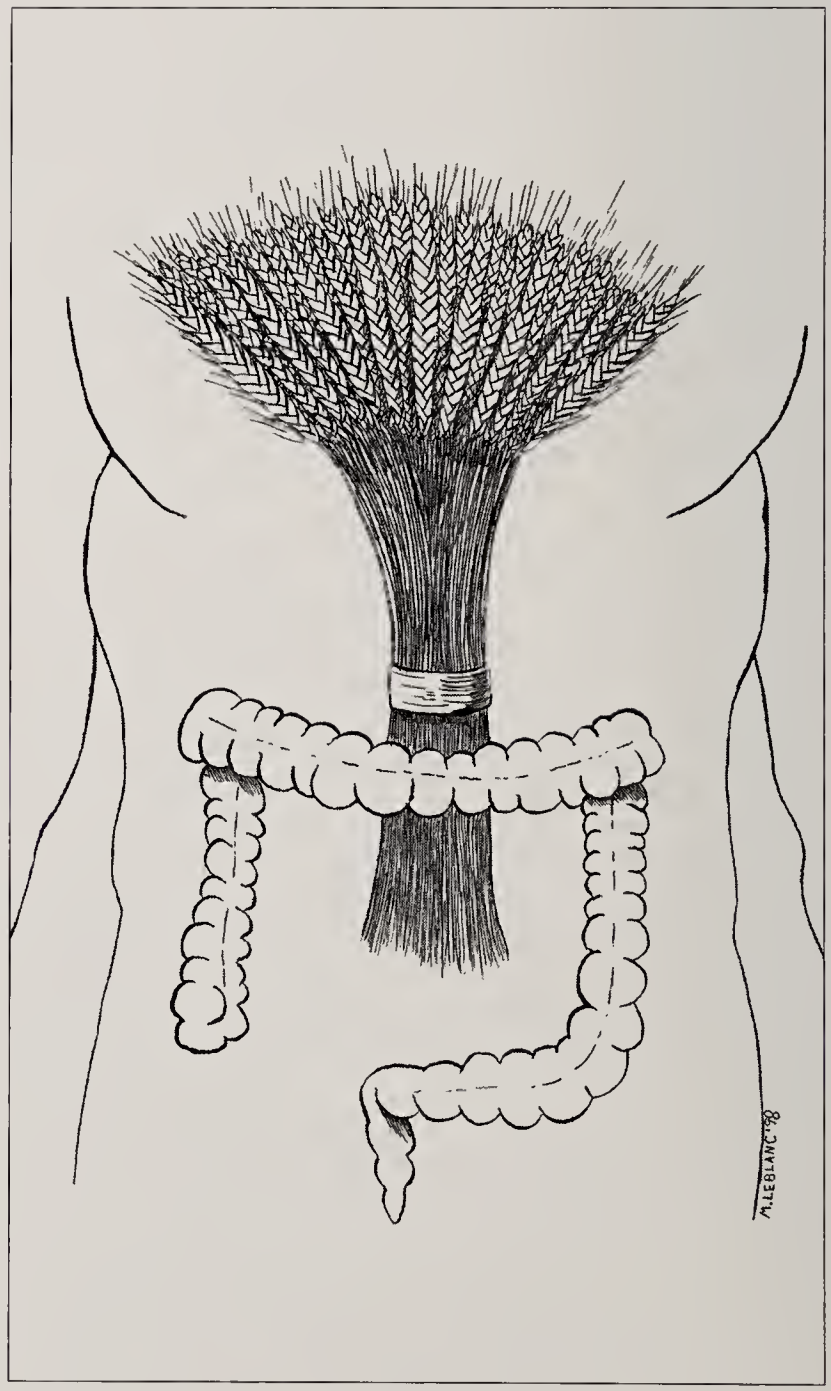
Abstract

Irritable bowel syndrome (IBS) is one of the most common but least understood gastrointestinal disorders. Its etiology, pathophysiology and treatment are poorly understood. One of the commonly used treatments for IBS is fibre and this review examines the current evidence for and against the use of fibre in the treatment of irritable bowel syndrome.

A Medline search, from 1975 to present, using the MeSH headings of "colonic diseases, functional" and/or "dietary fibre" was performed. Further data were obtained from the references of the relevant articles found in the Medline search. Seventeen publications were reviewed which consisted of four review articles on IBS, three review articles on dietary fibre, nine original clinical trials on fibre treatment for IBS, and one meta-analysis. Seven out of the nine studies showed that wheat bran, corn fibre and/or psyllium have no benefit over placebo in the treatment of IBS. The two studies that showed an effect over placebo involved ispaghula husk, a soluble fibre, and polycarbophil, a synthetic soluble fibre. One study suggested that bran may actually make symptoms worse. There was a very large placebo response rate in these studies ranging from 53%-71%. The conclusions of this review are the following: 1) IBS is a common gas-



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trointestinal disorder with a significant impact on the health care system; 2) Bran, corn fibre and psyllium do not demonstrate a significant benefit over placebo; 3) Ispaghula husk and polycarbophil demonstrate a significant benefit over placebo and warrant consideration; 4) a structured treatment plan provides significant symptom relief and accounts for the high placebo response of 53%-71%.

Introduction

Irritable bowel syndrome (IBS) is one of the most common but least understood gastrointestinal disorders.[1] It affects 10% to 20% of the adult population in developed countries.[2] The impact on the health care system is significant. IBS is common in family practice and accounts for over one-fourth of all referrals to gastroenterologists.[3]

Irritable bowel syndrome is defined as:
"A symptom complex of altered bowel habits, abdominal discomfort, and the absence of detectable organic disease".[1]

Its etiology and pathophysiology are poorly understood. There are no reliable physical findings or diagnostic tests. Therefore, the diagnosis is a clinical one based on the Rome criteria listed in Table 1. Unfortunately, the symptoms of IBS are similar to those of other more ominous gastrointestinal disorders. Thus, many unnecessary and expensive investigations may be performed before arriving at the diagnosis.[4]

Table 1
Rome criteria for the diagnosis of IBS

At least 3 months of continuous or recurrent symptoms including:

1. Abdominal pain relieved by defecation or associated with change in frequency or consistency of stool

AND

2. Altered defecation at least 25% of the time, including at least 2 of the following:
    * Altered consistency of stool (loose or hard)
    * Altered frequency of bowel movements
    * Altered passage of stool
    * Passage of mucous
    * Abdominal distention

For over 20 years, a high-fibre diet has been viewed as first-line treatment for IBS.[5] Since Burkitt linked a high-fibre diet to the low incidence of colorectal disease in rural Africa in 1972, reports of the wonderful benefits of dietary fibre have received much media attention.[6] Deficiency of fibre intake became a hypothesis for the pathogenesis of many diseases, including irritable bowel syndrome.[5, 6] However, is there scientific evidence for the use of fibre in the treatment of IBS or is it just a popular claim to treat a poorly understood disease? The aim of this paper is to answer that question.

Materials and Methods

A literature review of relevant material on the subject was performed. The material was found by a Medline search using the MeSH headings of "colonic diseases, functional" and "dietary fibre". Using the results of the Medline search as well as the references listed in some of the articles, a total of 17 articles were obtained and reviewed.

Results

The 17 articles reviewed consisted of four review articles on IBS,[1-4] three review articles on dietary fibre,[6-8] nine original clinical trials on fibre treatment for IBS ranging from 1976 to 1994,[5, 9-16] and one meta-analysis.[17] The meta-analysis by Klein [17] incorporated five of the original articles reviewed.[9, 11, 12, 13, 15] Table 2 summarizes the findings of the nine trials and one meta-analysis. Eight of the nine were randomized, double-blinded, controlled studies[9-16] and five of those were also crossover studies.[9, 10, 12, 14, 16] One of the nine was a retrospective, questionnaire study.[5] Three out of the nine studies used soluble fibre, such as psyllium (e.g. Metamucil),[11] ispaghula husk,[13] or polycarbophil.[16] Six of the studies used insoluble fibre, such as bran or corn fibre.[5, 9, 10, 12, 14, 15]

Seven out of the nine studies[5, 9-12, 14, 15] showed that wheat bran, corn fibre or psyllium have no benefit over placebo in the treatment of IBS, however there was significant symptom improvement in both treatment and control arms. Two studies showed a positive effect of fibre over placebo with ispaghula husk, in predominantly constipated patients,[13] and with the synthetic fibre, polycarbophil,[16] in patients with constipation or alternating diarrhea and constipation and particularly in patients with bloating as a major complaint. One study by Francis and Whorwell,[5] showed that 55% of their patients on bran reported worsening of symptoms and only 10% reported any improvement suggesting that bran may actually make symptoms worse. The meta-analysis by Klein[17] reported a 63-71% placebo response when pooling the results of the papers studied.

Discussion

Should dietary fibre be used for the treatment of IBS? The majority of the studies reviewed for this paper were randomized, double-blinded, placebo-controlled. However, there are some major limitations when interpreting the results. Most of the crossover studies did not have a wash-out period between the treatment and placebo arms allowing for contamination and misinterpretation of the results.[9, 12, 14, 16] With the popularity of fibre in everyday diet, the studies should have guarded against contamination via other dietary sources of fibre. Unfortunately, most did not do

this.[6, 9, 11, 12, 14-16] The studies had inconsistent inclusion criteria, no standardized symptom score tool, differing types and amounts of fibre and differing lengths of trial. All of these differences and limitations must be kept in mind when interpreting the results and making conclusions.

The Francis and Whorwell[5] study is the first and only study to suggest that bran, a popularly-used insoluble fibre, could be detrimental. This study was a retrospective study and was performed by a questionnaire given to 100 patients at a gastroenterology outpatient clinic. The patients were asked if their symptoms improved, worsened or remained the same when on various forms of fibre. There were no controls and no statistical analysis of the findings. Therefore, the conclusions from this study should be viewed carefully and further research is required.

The placebo response in the studies reviewed for this paper ranged from 53%-71%. We believe that the structured treatment plan, including the added medical attention and support the patients received during the studies, through frequent interviews and questionnaires, accounted for the favourable placebo response. The patients were given specific instructions and tasks to perform, such as daily symptom diaries. The studies acknowledged the disease as a real entity and empowered the patients by educating them, allowing them to reflect on their symptoms and share them with others and take an active part in their treatment. Although it may not have been the primary intention of the investigators, the study protocol provided a structured treatment plan which may account for the high placebo response rate. Such a structured treatment plan is practical and can be incorporated into any family physician's practice through frequent office visits, patient symptom diaries and questionnaires.

Dietary fibre is a heterogeneous group of non-starch polysaccharides that are relatively poorly digested.[8] The two main types of fibre are insoluble fibre and soluble fibre. Insoluble fibres include cellulose and lignin and common sources include bran, corn, and other plants. Natural soluble fibres include psyllium, ispaghula, pectin and guar and

Table 2
Published reports: Fibre and irritable bowel syndrome

Reference	Test Agent	n	Design	Conclusion
Solftot, 1976	wheat bran	59	R, DB,C	- improvement in 52% bran vs. 65% placebo; NS
Longstreth, 1981	psyllium	77	DB, C	- 77% psyllium vs. 71% placebo; NS
Arffman, 1986	wheat bran	20	R, DB, C, CO	- significant symptom improvement but no significant difference bran vs. placebo
Lucey, 1987	wheat bran	44	R, DB, C, CO	- 79% bran vs. 71% placebo; NS
Prior, 1987	ispaghula	80	R, DB, C	- 82% ispaghula vs. 53% placebo; SIGNIFICANT; especially in constipated patients
Cook, 1990	corn fibre	9	R, DB, C, CO	- significant symptom improvement but no significant difference between corn vs. placebo
Toskes, 1994 *	polycarbophil	23	R, DB, C, CO	- 71% preferred polycarbophil over placebo
Snook, 1994	bran	80	R,DB, C, CO	- 52% bran vs. 54% placebo; NS
Francis, 1994	bran	100	retrospective, Questionnaire	- 55% bran – worse; 10% bran - improvement
Klein, 1988 - Soltoft - Longstreth - Arffman - Lucey - Prior - Arthurs, 1983	wheat bran, ispaghula, psyllium		meta-analysis	- 63% to 71% placebo response

R = randomized; DB = double blinded; C = controlled; CO = crossover; NS = not significant (statistically)
** This study asked patients to choose between the 2 treatment arms and 71% preferred the polycarbophil*

common sources include oat products, dried beans and certain fruits and vegetables.

Polycarbophil is a synthetic soluble fibre that exerts its maximal hydrophilic activity in alkaline environments such as the small intestine and colon.[16] It is interesting that the two fibres that show a benefit over placebo, ispaghula and polycarbophil, are both soluble fibres. None of the studies specifically compared insoluble to soluble fibres in the treatment of IBS. Some hypothesize that soluble fibres are better than insoluble fibres because they can benefit both constipation-predominant and diarrhea-predominant patients.[8] Some soluble fibres may help reduce the looseness of stool because the breakdown products, short-chain fatty acids, enhance water and sodium absorption.[8] Polycarbophil causes less gastric distention because it has minimal action in the acidic environment of the stomach.[16] Furthermore, experiments in dogs showed that polycarbophil meals do not increase small intestinal motor activity and were associated with aborally directed jejunal contractions, which is in contrast with pectin and psyllium meals which increase small intestinal motor activity and produce irregular jejunal contractions.[16] This may account for the decreased flatulence and bloating seen in humans when using polycarbophil compared to other insoluble fibre laxatives.[16] The above mechanisms may explain the benefit seen with the use of polycarbophil in the treatment of IBS. However, it is still unclear why ispaghula, a natural soluble fibre, shows benefit when other natural soluble fibres, such as psyllium, do not.[11]

Should dietary fibre be used for the treatment of irritable bowel syndrome? Based on our review of the literature, we offer the following conclusions and recommendations:

1. IBS is a common gastrointestinal disorder with a significant impact on the health care system.
2. Bran, corn fibre and psyllium do not show any benefit over placebo in the treatment of IBS. In fact, it has been suggested that bran may make the patient's symptoms worse.
3. Ispaghula husk and calcium polycarbophil do show significant benefit over placebo in the treatment of IBS.[13, 16] Ispaghula husk was particularly effective in predominantly-constipated patients. Calcium polycarbophil was effective in patients with constipation or alternating diarrhea and constipation and may be particularly useful in patients with bloating as a major complaint.
4. A structured treatment plan with increased frequency or duration of patient contact and counseling can provide significant symptom relief and account for the high placebo response rate of 53-71%. These studies had strict protocols which required the patients to maintain symptom diaries, attend frequent interviews and complete many questionnaires. We believe that the medical attention and support the patients in the studies received was very beneficial to them. This structured treatment plan can be effectively incorporated into a family physician's practice.

Further research is required on this subject. An appropriate study would compare a group treated with ispaghula husk or calcium polycarbophil plus a structured treatment plan to a control group that would only receive a structured treatment plan with frequent interviews, questionnaires and symptom diaries but no fibre supplement. A meta-analysis incorporating more recent trials would be useful as well as a trial to prove or disprove the claim set out by Francis and Whorwell *et al.* regarding bran's possible detrimental effect.[5] A comparison between soluble and insoluble fibre in the treatment of IBS would also be helpful. These are just some of the possibilities for future research to answer the question, "Should dietary fibre be used in the treatment of irritable bowel syndrome?"

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Moving Doctors North

David Kaplan, MSc. (0T1)

The health care system in Ontario is facing two crises. Healthcare expenditures account for approximately nine percent of the Gross National Product of Canada, a higher percentage that any other affluent OECD[a] country.[1] Moreover, many Northern Ontario communities suffer from a shortage of physicians. To combat these crises the Ontario government has toyed with restricting physician-billing numbers in over-serviced urban areas. Under current case law,[b] it seems that Canadian provincial governments can restrict medical professionals from practicing in over-serviced areas; whether this policy option is ethical remains unclear. In *Wilson v. Medical Services Commission of British Columbia,*[c] the court found an attempt at such a restriction in British Columbia to infringe on a physician's section 7 liberty right, which is found in the *Canadian Charter of Rights and Freedoms.*[d] In *Agricultural Credit Corp. of Saskatchewan v. Mielke*[e] however, Justice Lamer asserted that the court's argument in *Wilson* was questionable; the majority of the Supreme Court decided that the section 7 liberty right does not encompass the right to practice one's profession. Since the Supreme Court of Canada has found that the British Columbia Supreme Court wrongly interpreted the *Charter's* liberty clause, it would seem that an examination of *Wilson*

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a Organization for Economic Cooperation and Development, (OECD), international organization, formed in 1961. The organization has 25 full members, including Australia, Britain, Canada, France, Germany, Japan, Mexico and the U.S. Members pledge to work to promote economic growth, aid developing nations, and expand world trade.

b This paper does not comment on the recent decision of the Supreme Court.

c *Wilson v. Med. Services Commission 30 B.C.L.R. (2d)*; hereinafter, *Wilson*

d Hereinafter, the *Charter*

e Hereinafter, *Mielke*

would be moot; the Canadian Supreme Court rejected its argument. Yet, I argue that an examination of the issues raised by the parties in *Wilson* can guide the ethical discussion and highlight a moral right of physicians to practice their profession. Before the government can adopt this regulatory policy, it must fully assess the ethical implications of restricting a physician's ability to practice medicine.

The Issue

Canada is faeing a debt erisis. Northeott, in "The Polities of Fiseal Austerity and Threats to Medieare", argues that an increasing proportion of Canada's Gross Domestie Produet [GDP] is spent on servieing the debt.[2] The servieing of this massive debt, eaused by the operating defieits of the 1970s and 1980s, eaused a diversion of revenue to pay for debt finaneing. The diseussion over the publie debt has led the government to politieize the debate over social serviee resourees.[2] This paper will speeifically examine healtheare resourees. The government has blamed eonsumers and medieal serviee providers for increased healthcare expenditures. Out of all industrialized eountries, Canada spends the seeond highest percentage of its gross domestie produet (GDP) on healtheare. Yet, Canadians do not enjoy longer nor healthier lives than eitizens of other industrialized eountries, which spend less money on healtheare. While Canada spends (per eapita) the seeond highest amount of GDP on health, it does not rank among eountries with the highest health outeomes.[3] Clearly government must lower health expenditures, or expeet higher outeomes. Due to the eurrent fiseal elimate, the former option has been seleeted as a poliey goal.

Certain provineial governments have deeided that regulating the practice of those professions paid for by government ean reduee soeial serviee expenditures. These governments have frozen spending on healtheare; some of the legislative assemblies have even eut funding. The British Columbia government in 1985 introdueed amendments to the *Medical Services Act* whose praetieal implications limited the ability of a physieian to partieipate in the medieal insurance plan[f] and restrieted the geographie loeation in whieh the doetor eould practiee. This implieitly restrieted the physician's ability to praetiee his/her profession full-time (*Wilson* 1988).

The eurrent government of Ontario has adopted similar policy goals. Shortly after taking offiee, the Conservative government passed Bill 26. The relevant highlights of Schedule H of Bill C-26 read as follows:

- Permits the government to unilaterally define an insured serviee, and set fees for the provision of those serviees. Factors determining fees inelude physieian speeialty, experienee, and geographie loeation.
- Permits the government to unilaterally determine what eonstitutes an "eligible" physieian for purposes of obtaining a billing number. Criteria to determine eligibility inelude requirement for speeialists to have a hospital appointment and for family physieians to work in areas that are not "oversupplied."
- Allows health minister to impose a moratorium on "eligible" physieians and billing numbers.
- A government deeision to determine that a physieian is not eligible eannot be ehallenged by legal aetion.
- Opted-out physieians ean be required to submit aeeounts direetly to OHIP for eertain periods in eertain eireumstanees.
- Provides the health ministry with new investigative powers whereby inspeetors ean enter and inspeet a physieian's offiee without a warrant (whieh is only required for entry to a private residenee) and colleet reeords (*Bill 26 (Omnibus) Summary* 1995)

The Ontario government believes that these measures will reduee health services expenditures by, among other means, lowering the number of operating doctors in over-servieed, urban areas. In order to reduce budget defieits, the Ontario government wishes to eut spending in the soeial serviee sector by regulating the medieal profession.

Bill Vander Zalm's government introdueed amendments to the British Columbia *Medical Services Act* whose practical implieations severely regulated the medieal profession (*Wilson* 1988). The British Columbia Supreme Court instrueted the British Columbia government that it eould not control healthcare expenditures by regulating the medieal profession in this manner. The eourt found that this aetion violated the *Charter's* liberty provisions. Yet, given the eurrent fiscal and health erisis in Ontario would such a deeision be reached if the provineial government were to invoke the powers it has under Bill 26? Should the Ontario government use regulatory provisions as a eost-eutting vehiele to lower its healtheare expenditures? To this end, the *Wilson* judgement of the British Columbia Supreme Court must be examined and its impaet on the Ontario government's options must be assessed.

LEGAL ANALYSIS:
Wilson v. Medical Services Commission

Case History

In 1983, the British Columbia government passed Bill 24, legislation that was to be followed by an enaetment entitled the *Medical Services Act*. This bill was never enaeted, but the government implemented the same regulatory framework it

f In Canada, the provincial governments each have health/medical insurance plans that reimburse doctors for the medically necessary services they provide to insured individuals. These insurance plans are financed jointly by the federal and provincial governments.

would have made into law. The government established a new scheme for distributing physician practitioner numbers (referred to a billing numbers). Physicians needed to apply to the *Medical Services Commission* for a billing number. The *Commission* considered each application by examining whether the medical services offered by the applicant were needed in the area. The regulations precluded consideration of the applicant's current or former residence. This scheme only affected physicians who did not have billing numbers under the existing provincial insurance plan.

Dr. R. Mia challenged the government's actions. The trial court judge found that the did not have the authority to operate the government's scheme under the *Medical Service Act* 1979.[g] Chief Justice McEachern found that Dr. Mia's sections 6(2)(b) and 7 *Charter* rights[h] were violated by the regulatory framework. McEachern asserted that since the scheme was not legislated it could not be saved under the *Charter* 'reasonable limits' clause.[i] The government did not appeal the trial court's decision. Instead in 1985, it passed amendments to the *Medical Services Act* 1979 that gave legislative effect to their earlier regulatory framework. The applicants (Drs. Wilson, Maxson, Arnason, and Conway) in *Wilson* either had been denied a billing number under the plan, had been granted a billing number that restricted their practice to a certain geographic area, or had been granted a *locum tenens* number but denied a permanent one. They contended that the *Medical Services Act*, as amended in 1985, denied them the right to practice their profession. They argued that based on *Mia* this right was found in the section 7 liberty clause of the *Charter*.[j] At trial, Justice Lysyk disagreed with a part of the McEachern's reasoning in *Mia* and ruled against the doctors.

The Legal Question

On appeal to the British Columbia Supreme Court, the question of law was: Is the scope of section 7 of the *Charter* broad enough to encompass the opportunity of a qualified and licensed professional to practice his or her chosen profession "without restraint as to place, time or purpose?" (*Wilson*, p. 12) If the court should find that the liberty right guaranteed in section 7 is that broad, it must decide if the regulation can be saved under section 1. The following discussion will not follow the legal reasoning in *Wilson* verbatim. Rather, using the *Wilson* judgement as a template, it will explore the concepts of liberty and fundamental justice, as they apply to the regulation of medical practice by restricting physician billing number in urban areas.

Liberty Rights

Definition

Chief Justice Dickson stated that the judiciary should apply a generous definition to section 7 of the *Charter*. The *Charter* provides that:

> s. 7 Everyone has the right to life, liberty and security of person and the right not to be deprived thereof except in accordance with the principles of fundamental justice.

In general, a particular liberty is a complex combination of rights and duties. Not only does liberty afford the individual the permission to do or not to do something, it requires that government and other people not obstruct the individual from pursuing her goals and aspirations.[4] These rights are equal *opportunities* to liberty; they do not ensure *outcomes*.

Following in the tradition of this "generous rather than legalistic" (*R. v. Big M. Drug Mart Ltd.*, [1985] 1 S.C.R. 295) definition, the court, in *Wilson*, defined 'liberty' as including the "individual freedom of movement, including the right to choose one's occupation and to pursue it." (p.15) According to Madam Justice Bertha Wilson in *Morgentaler*, liberty is "inextricably tied to the concept of human dignity." (*R. v. Morgentaler*, [1988] 1 S.C.R. 30, p.20) S. 7 confers on the individual a measure of autonomy in important decisions concerning his own life. This new context for liberty results from looking at 'work' as a fundamental part of a person's life. Not only does employment allow the individual to sustain himself, it provides the person with a role in society. Thus, employment is essential to an individual's sense of selfhood and happiness (*Ref. Re Public Service Employee Relations Act (Alta.)*, [1987] 1 S.C.R. 313). Moreover, a vocation is a vehicle through which society allows a person to become a constructive member of that community, one who contributes to the overall good. As such a device, it can be seen as providing "recognition of the individual's being engaged in something worthwhile." (*Wilson*, p.16) The section 7 right to liberty has been characterized as a rich freedom that even entitles one to pursue one's chosen occupation.

Fundamental Justice Issue

While this proposed regulation of medicine seems *prima facie* to be a violation of a right to liberty, this right can be suspended 'in accordance with the principles of **fundamental justice**'.[5] The issues of deprivation and the principles of fundamental justice, in general, are the second part of an analysis of s. 7. One must now briefly look at how the court defined 'fundamental justice' and check whether or

g *Mia v. Medical Services Commission of British Columbia*, (1985) 61 B.C.L.R. 275; hereinafter, *Mia*.

h Section 6(2)(b) of the *Charter* guarantees rights, which include the right "to pursue the gaining of a livelihood in any province. Section 7 will be discussed in greater detail below.

i The *Charter* guarantees the rights in it only to a reasonable limit. A discussion of section 1 will follow below.

j The appellant physicians also argued on the basis of ss. 6 & 15 of the *Charter*, but the discussion in this paper will focus solely on the argument from liberty.

not the regulatory measures under investigation violate this principle.

What is Fundamental Justice?

Canadian courts have defined fundamental justice as the context for the rights guaranteed in section 7. The term is not synonymous with 'natural justice'. Since natural justice refers only to procedural justice, such a definition would leave the *Charter's* liberty provisions in "a sorely emaciated state." (*Re: Motor Vehicle Reference*, [1985] 24 D.L.R., 548) Fundamental justice refers both to procedural and substantive justice. According to Madam Justice Bertha Wilson and Justice Antonio Lamer, the principles of fundamental justice cannot be exhaustively defined. These ideals are found in the basic tenets of our legal system. As such, judges best define them since they have the greatest understanding of the Anglo-European legal tradition. The principles of fundamental justice are qualifiers of the rights to life, liberty and security of person as affirmed by section 7.

Are the Regulations at Hand Fundamentally Just?

The regulation of medical practice violates fundamental justice by denying the right to practice instead of managing practice. There have been cases in which the regulation of professions was found to be constitutional.[k] Had the regulations been set up to manage and control the practice of medicine, they could take away the liberty to practice within the scope of fundamental justice. In *Wilson*, the court clearly stated that legislation that regulated the standards of admission, mandatory insurance, and standards of practice would not infringe on s. 7. The practical outcome of the regulation enacted by the British Columbia legislature, however, outwardly denied doctors the right to practice. Doctors cannot be expected to practice privately. According to the data presented in *Wilson*, ninety-nine percent of the population in British Columbia subscribes to the provincial health plan. Would Canadians, who are covered by a universal and comprehensive public insurance plan, go to private-funded doctors and pay for services out of their own pockets? In *Wilson*, the court argued that regulations that restrict access to insurance billing numbers implicitly deny physicians the liberty to practice medicine, and cannot be administered within the principles of fundamental justice.

Wilson and its Applicability to Other Jurisdictions

The applicability of previous legal decisions to other cases is dealt with in common law by the doctrine of *stare decisis*. *Stare decisis*, the doctrine of precedent, requires that lower courts respect the decisions of higher courts in the same jurisdiction. Decisions by courts outside of the jurisdiction of the court facing a new case are not binding. Rather, they are persuasive; the judiciary uses them to build its legal arguments. Following precedent ensures continuity and prevents a plethora of rulings on the same issue.

Would *Wilson* apply in Ontario? It was decided by the Supreme Court of British Columbia and therefore the decision is not binding on other provinces. On appeal to the Supreme Court of Canada a reversal of decision would have been possible. Moreover, the British Columbia government did not invoke a section 1 defense to save the *Medical Services Act* as amended in 1985. Even if the court found that a similar move by the Ontario Government's to regulate medical practice contravened the liberty provisions of the *Charter*, the government may have a sufficiently pressing legislative objective. A section one defense could allow them to regulate billing numbers even though the British Columbia court argued otherwise.

Yet, the Canadian Supreme Court in its ruling in *Reference Re ss. 193* and *195.1(1)(c) of the Criminal Code*[l] challenged the validity of the *Wilson* decision. In *Reference*, the Supreme Court of Canada held that the relevant sections of the Criminal Code of Canada that prohibit solicitation for prostitution, are reasonable limits on an individual's right to freedom of expression. Moreover, the Criminal Code, according to Justice Lamer, does not offend section 7 of the Charter, since section 7 does not include the right to practice one's profession. Justice Lamer argued that the *Wilson* decision's distinction between the right to work, which is purely economic, and the right to pursue a profession, which is characterized as encompassing one's dignity and sense of self-worth is unfounded. The *Wilson* judgement erroneously relied on the dissenting opinion of the Chief Justice in *Reference Re Public Service Employee Relations Act* in making this distinction. The Chief Justice wrote:

> It has been suggested that associational activity for the pursuit of economic ends should not be accorded constitutional protection. If by this it is meant that something as fundamental as a person's livelihood or dignity in the workplace is beyond the scope of constitutional protection, I cannot agree. If, on the other hand, it is meant that concerns of an exclusively pecuniary nature are excluded from such protection, such an argument would merit careful consideration. In the present case, however, we are concerned with interests which go far beyond those of a merely pecuniary nature.
>
> Work is one of the most fundamental aspects in a person's life, providing the individual with a means of financial support and, as importantly, a contributory role in society. A person's employment is an essential component of his or her sense of identity, self-worth and emotional well-being. Accordingly, the conditions in which a person works are highly significant in shaping the whole compendium of psychological, emotional and physical elements of a person's dignity and self respect.

k Examples of such cases are Noyes v. Bd. of Sch. Trustees, Beltz v. Law Society of BC 7 B.C.L.R. (2d) 353. (1987) 1 W.W.R. 427 and Isabey v. Man Health Services Comm.

l *Reference Re ss. 193* and *195. 1(1)(c) of the Criminal Code*; hereinafter *Reference*.

In *Wilson*, the court notes that although the issue in the *Reference* case did not deal with section 7 of the *Charter*, the Chief Justice's dicta emphasizes that the opportunity to pursue one's own profession should be afforded constitutional protection as an aspect of liberty under s. 7 of the *Charter*. Lamer asserts that the Chief Justice in *Reference Re Public Service Employee Relations Act* had no such intention. The issue at hand was not whether the right to work or pursue a profession existed. Rather, that the "right to bargain collectively and to strike was essential to the capacity of individuals to ensure equitable and humane working conditions". (*Reference*, p.94) According to Justice Lamer, the right to practice one's profession is not guaranteed by the *Charter*.

Since the section 7 liberty right does not include a constitutional right to practice one's profession, a section 1 'reasonable limits' defense becomes moot; no *Charter* right is offended. While a constitutional right to pratice one's profession does not exist, I contend that the court's discussion in *Wilson* persusively argues for such a moral right. Therefore, exploring whether or not these regulations are 'pressing and substantial in a free and democratic society' becomes important in that such a discussion will flesh out the ethical issues involved in the political debate surrounding healthcare expenditure containment by regulating fee-for-service medicine.

Ethical Analysis

Although it seems that government can restrict physician billing numbers without offending the *Charter*, whether this practice is ethical remains to be examined. According to Lord Devlin, no society can exist without shared politics, morals and ethics. He states that law should be a reflection of a fundamental agreement about what is good and what is evil, what is right and what is wrong. Yet, others argue that everything legal is not necessarily ethical. A right to practice a profession (medicine, for example) is not guaranteed by the *Charter* and, therefore, the state can restrict physician's ability to practice by not issuing billing numbers in overserived, urban areas. I contend that a practical ethical analysis will illustrate that while 'constitutional' and 'legal', this policy action is not ethical.

Are Medical Professionals Entitled to such a Right?

The first portion of this ethical analysis will demonstrate that the practice of medicine, while self-regulated by a professional body, is synonymous with carrying on a trade, simply trying to make a living. While the right to practice the profession that one chooses for oneself does not fall within the rubic of liberty in the *Charter*, one can still argue on ethical grounds that individuals should be allowed to practice their chosen profession. The court in *Wilson* indiscriminately linked the practice of a profession with simply trying to make a living, but it is necessary to establish that these two forms of employment are equal in this respect. A reliance on Marxist theory will assist in this argument.

In some respects it seems that society considers medicine to be an 'elevated' profession. This is mostly due to medical dominance. Medical dominance is defined as the effective stronghold that medicine has achieved on the healthcare profession hierarchy.[6] Medicine poses a technical body of knowledge that is not accessible to the public. Medical dominance emerged in the late nineteenth century and had attained its hold by the early twentieth century. This stronghold had been realized by four factors.[6] First, physicians had the support of the state and persuaded the government to license the practice of medicine. This licensing led to the gradual exclusion of other medical and quasi-medical professions. This exclusion of other 'lower status' fields, such as midwifery, led to medicine's monopoly on healthcare. The creation of the Canadian Medical Association in 1867 allowed the profession to evaluate itself and to effectively police its own members.[6] Second, the introduction of public health insurance further excluded those health professions not covered by the government's fee schedules. Third, the individual doctor-patient relationship has had social ramifications on the perception of the health professions. Patients need doctors. This creates an unequal relationship between the two; doctors emerge on the top of this social relationship. Lastly, it has been argued that medicine's power over the 'subordinate' healthcare professions exists because it serves capitalism.[7] Capitalism lodged onto a medical view of disease that focuses on biological causation in opposition to a social-model of disease.[7] Government supported medicine because it reproduced the class structure and ideologics of the capitalist state.

While it seems from this brief exploration of medical dominance that physicians cannot affiliate themselves with the rest of the working class, they are undergoing a process which closely links them with the rest of the laboring class. Three factors have contributed to the 'proletarianization' of medicine.[8] Early in the development of the medical profession, the governing body allowed the corporate sector to enter into the drug market. This opening has expanded to allow corporations into all market areas, including surgical and hospital supplies. This infiltration of the corporate world into medicine began the gradual wearing down of the profession's control over the means of its labour.

The second factor in the profession's 'deprofessionalization' is due to the bureaucracy created in the hospital setting.[8] The hospital, which originally was required to house the

myriad of medical procedures and tests, established an upper administration to maximize its efficiency. This administration, which wishes to curb expenditures, is often at odds with the medical profession that wants to expand care and treatment.

Finally, dehumanized care, which resulted from overspecialization, has given rise to a powerful consumer movement that seeks to challenge medicine's dominant position.[8] They want doctors to take a comprehensive approach to disease treatment. All patients expect their doctors to be honest and straightforward when giving advice. Patients want to be respected. Most importantly, they insist that they be better informed so that they can make autonomous decisions about disease management and health. A physician may prescribe medication, but ultimately patients now make the final informed decisions about their own care.

While historically it may have seemed that medicine, a self-regulated profession, was quite different than other forms of labour, it is now understood that doctors face many of the same difficulties as other common workers. The issue at hand is not the regulation of an industry. Governments must be allowed to regulate some sectors of private enterprise when public interests are involved. Canadian governments do not wish to manage the province's health care system. Rather, they will prohibit workers from practicing their chosen profession. Moreover, doctors have not argued that the character of the infringed liberty right is economic in nature. Being granted a billing number does not guarantee an income in over-serviced areas. For example, a young physician who opens a new Toronto practice at the Bay and College intersection will be hard pressed to find new clients. In Wilson, the judiciary correctly linked the practice of a profession with carrying on a trade. Thus, government regulations that limit a doctor's liberty right *to practice his/her profession are prima facie* invalid.

Section 1 as a Model for Practical Ethical Analysis

Since the purpose of this investigation is not to determine how courts should attempt to resolve the issue of government regulation of professions in terms of cost cutting, a full analysis of the section 1 test is not warranted. Moreover, the government would not need to invoke such a defense, because no right has been infringed; the right to practice one's profession is not found in the scope of section 7. Surveying the data that both the government and the medical profession would provide for such an analysis, however, it will both illustrate the practical political realities of health cost-containment in Canada, and inform an ethical analysis of the issue. Section 1 discussions highlight whether government legislation is 'pressing and substantial in a free and democratic society.'

s. 1 The Canadian Charter of Rights and Freedoms guarantees the rights and freedoms set out in it subject only to such reasonable limits prescribed by law as can be demonstrably justified in a free and democratic society.

The *Charter* guarantees the rights in it only to a reasonable limit. Once a government law is found to infringe on a right protected by the *Charter*, the state can request that section 1 be used to 'save' the offending legislation. In a section 1 discussion the court must ask the following questions (as defined in *R. v. Oakes*, 26 D.L.R. (4th), p. 240)[m] a: Does the objective of the regulation "relate to a concern which is pressing and substantial?" In this first part of the '*Oakes*' test, the court must decide if the legislative concern, which offends the right of a particular individual or group,. Should the regulation pass this portion of the test, the court must then ask whether the means chosen to address the significant objective are "reasonable and demonstrably justified." This involves a three-part proportionality test. Are the means chosen rationally connected to the objective? Do they impair the individual's right as little as possible? Is a proportionality struck between the effects of the measures which are responsible for limiting the *Charter* right or freedom, and the objective which has been identified as being sufficiently important? The 'reasonable limits' clause allows the court to balance the freedoms guaranteed in the *Charter* against the concerns of a democratic society. In effect, section one balances the rights of the individual and society using a practical ethical analysis.

The following practical ethical analysis will discuss the physician's moral right to practice medicine in light of government's call for curbing healthcare costs. A reliance on section one as the framework for this analysis is useful in that it allows deontological claims to be restricted when societal concerns are pressing. Such an analysis, however, focuses on justice and relies on the language of the law; therefore, it frames the discussion in a specific manner and narrows its scope. The ethical analysis could take other forms, such as an ethic of care analysis. Such an analysis would examine the relationships affected by the government's regulatory scheme. Issues such as religion, occupation of the spouse, education and socialization of children of the affected physician need to be examined in such an inquiry. Given its practical nature, section 1 is used here as the framework for the ethical discussion.

m *R. v. Oakes*, 26 D.L.R. (4th); hereinafter, *Oakes*.

Government: The Fiscal Crisis - a 'Pressing and Substantial Concern'!

The Canadian federal and provincial governments assert that they need to control public spending, in part, by curbing healthcare costs. They argue that it is a valid concern of government. All levels of Canadian government are experiencing a fiscal crisis that is resulting in budget cuts to social services, healthcare included. The government spending of the early- to mid-1980s has resulted in a deficit crisis.[2] The Ontario government spends eighteen percent of its GDP on servicing the debt; the Federal government spends thirty-seven percent of its GDP on debt servicing.[9] The public debt is so large that, in order to pay the interest charges, the government must go into a deficit each year. Government budgetary constraints in health care are a result of servicing the national debt.

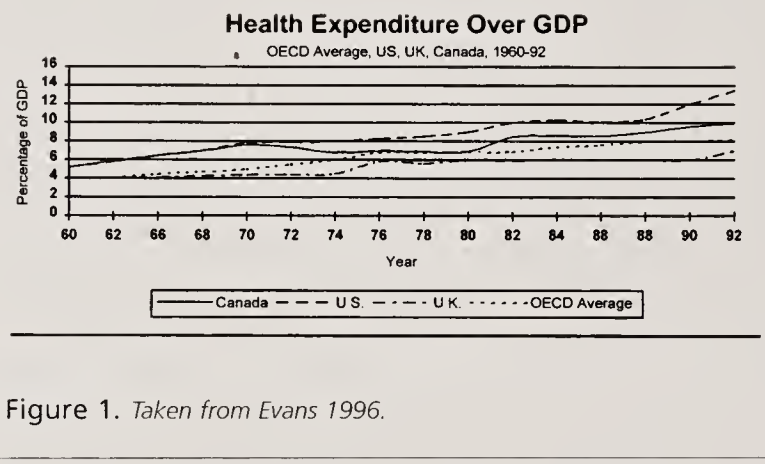

Figure 1. *Taken from Evans 1996.*

Government believes that healthcare spending is out of control. Healthcare is one of the largest public expenditures. Canadian public spending for healthcare went $700 million over budget in 1994.[19] That year government spent $2,478 per person ($72.5 billion) on healthcare. These healthcare expenditures accounted for 9.7% of Canada's GDP. The three largest expenses in this budget were hospitals (37.3%), physicians (14.2%) and drugs (12.7%). Public sector spending accounted for 71.8% of these total health resource expenditures. Federal health transfers accounted for thirty-three percent of provincial government health expenditures; the provincial government came up with the remainder.[19] Ironically, while Canada spends the second highest percentage of its GDP (of all OSED countries) on healthcare, Canadians do not enjoy better and healthier lives than citizens of countries who spend less money on healthcare (Figure 1).[1, 3] Japan, the country with the highest health outcomes, spends the lowest percentage of GDP (below eight percent on healthcare). Recent commissions have concluded that the healthcare system does not suffer from under-funding.[1,18] In essence, governments in Canada have stated that they are finding fee-for-service medicine troublesome, and they blame physicians for over-prescribing services. Ottawa and the provincial legislatures have argued that there must be a reduction in utilization of healthcare resources. Until recently, however, the government has not attempted to control individual physician billing.

Since government is set on putting Canada's economic house in order, the 'fiscal crunch' outlined above has placed universal healthcare in the balance. Fiscal responsibility through cost control is an appropriate goal for government. Lawmakers must protect Canada from large deficits that negatively impact on foreign investments. The federal government cut its share of the medicare budget from fifty percent of the national total in 1977 to approximately twenty-two percent in the current year.[11] According to the Federal budget of February 1995, this funding will be reduced by an addition $5.3 billion over the next two years. The governments contend that Canadians express support for medicare as an 'untouchable' public good; yet, they are unwilling to pay more for it through taxes.[11] In this light, the provincial governments have looked to different ways of cutting health costs.

Governments have resorted to stricter regulations of social services, specifically healthcare. The BC provincial government argued in *Wilson* that each new doctor in an urban centre costs the province a certain amount of money. Since it seems that the number of doctors in a specific area influences an insatiable public appetite in Canada for healthcare, they therefore attempted to regulate the number of doctors who could bill the provincial health plan.

In Ontario, similar legislation has been enacted. The Ontario government also claims that Northern Ontario communities are poorly staffed by medical professionals and lack specific health services. Bill C-26 marked the breakdown of co-operative care of the health system by the Ontario Medical Association and the provincial government.[12] The provincial governments argue that attempting to lower healthcare spending by curbing billing to provincial health insurance plans is an appropriate and legitimate action. They argue that not only is the containment of health spending a 'pressing and substantial concern', but the means employed by provincial governments are 'rationally connected' to this objective. They have a responsibility to lower the provincial debts. Reducing fees paid to a physician, which account for the second largest health related expense, is a practical way of accomplishing this task.

Physicians: Right to Liberty and Health Gap

Physicians and the provincial medical associations could theoretically argue that while the proposed regulatory means may be 'rationally connected' to the government's legislative objective, they do not impair the rights of physicians *as little as possible*. The legislative measures adopted by British Columbia and Ontario governments effectively prevent physicians from practicing medicine. Practically, they force some doctors to practice privately. As noted earlier, almost all Canadians subscribe to the provincial health plans. Regulations that restrict access to insurance billing numbers implicitly deny some physicians the liberty to practice medicine.

Not only do these proposed government regulations practically deny physicians the liberty to practice medicine, but more importantly they also cause an expansion of the health gap that exists between high- and low-income Canadians. Canada's present healthcare system, federally 'controlled' by *The Canada Health Act* (1984), has maintained a 'health gap' that separates poor and wealthy Canadians. Prosperous Canadians live longer and healthier lives than low-income Canadians.[13]

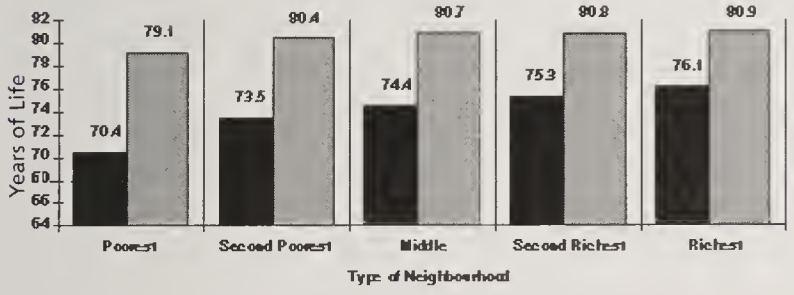

Figure 2. *Taken from Health, Healthcare and Medicine, 1990.*

This gap can be measured by two standards, life expectancy and health expectancy. The latest study in life expectancies (figure 2) from 1986 relates deaths in major cities to residents of different types of neighbourhoods.[14] It reveals that, on average, males who resided in the poorest neighbourhoods lived 70.4 years, whereas males who inhabited the richest areas lived 76.1 years (a difference of 5.7 years. The 'health gap' between females is not as pronounced; those in poor areas lived 79.1 years, and those in the richest regions lived 80.9 years.

As enlightening as these statistics are they may be misleading. Deaths in poor neighbourhoods are linked to violence and crime, as well as health. An earlier study from 1978, however, is based on individual rather than neighbourhood income. The life expectancy of those in the lowest income bracket was 71.9 years, whereas individuals in the highest income group lived on average 76.4 years.[n] "It is clear that people of lower-income groups and with lower levels of education do not enjoy the same level of health as those Canadians of higher social and economic status."[14] The analysis of data on health expectancy corroborates this statement. Health expectancies compare the degrees of health among people of different income groups. Canadians of the lowest income group lived 54.9 years without restrictions on their activities (considered good health). The number of years of good health increased as incomes increased; it reached 65.9 years of good health for those in the highest income bracket.

Russel Wilkins of the Canadian Centre for Health Information best interprets the implications of this data.

> Based on the best data currently available in Canada, it appears that the health problems of the poor children begin before birth and continue to place these children at risk of death, disability and other health problems throughout infancy, childhood and adolescence.[14]

The Canada Health Act (1984), created in response to factors that were interfering in reasonable access (the imposition of extra-billing by physicians and user-fees by hospitals) "is not providing accessible and appropriate health services for all."[13] It maintains the wide gap between the relative health of low- and high-income Canadians.

The Canadian government has recognized this 'health gap' for a long time. A 1986 publication by Health and Welfare Canada, *Achieving Health for All: A Framework for Health Promotion*, affirms that:

> The first challenge we [the Canadian government] face is to find ways of reducing inequities in the health of low- versus high-income groups in Canada. As we search for health policies which can take this country confidently into the future, it is obvious that the reduction of health inequalities between low- and high-income groups is one of our leading challenges.[15]

The Canadian government has made a commitment to reducing the health gap. Now, it must determine how it is to approach this task.

Regulating the number of doctors in urban areas will not close the health gap. In fact, this form of regulation will widen it. Provincial governments must currently adhere to

n Study by Statistics Canada and the Canadian Institute for Advanced Research. The Study related deaths to individual earnings over a period of years among men 65 and older who had contributed to the Canadian Pension Plan. These date cover half a million individuals, and for each individual data from almost a quarter of their lives have been drawn upon.

the tenets of the *Canada Health Act*, 1984. Healthcare in Canada must be universally accessible; currently, the above-cited documents show that it is not the case. The first law of cost-control is that shifting costs to other people (privatization) is easier than curbing costs.[16] While the government says that they "are convinced that Canadians want a publicly administered comprehensive system that is universally accessible across the country,"[20] their legislative measures will effectively create a two-tier health system. British Columbia government-style legislation attempts to push more doctors into private-funded practice. In theoretical terms, it has been shown that such a system cannot be viable, yet others believe that prosperous Canadians would be willing to pay 'out-of-their-pocket' for medical services.[11] Such a system could develop very quickly into an American multiple-payer system that leaves the Canadian system "less equitable, more costly and less efficient."[11] To paraphrase Robert Evans, the American model is a model of what not to do.[1] If wealthy Canadians are serviced by private facilities, there will be less public pressure to keep up the standard of care in the publicly funded sector of the system.[17,18] Moreover, the powerful voices in the Canadian public sphere would no longer call for significant efforts to enhance health awareness and disease prevention programs. Bill C-26 allows the government to decide where physicians can practice; they decide, without advice from the health profession, what geographic areas are suffering from underfunding. The health-gap is not confined to specific geographic locations; rather it is contingent on individual income.[12,17] Prohibiting doctors from practicing in major urban centres will severely deter the quality of care in inner-city areas. Clearly, such a private-public system would widen the health gap.

In summary, a deeper analysis reveals that this type of regulation is not the least restrictive way of achieving the goal of the government; it practically denies physicians the ability to practice. Perhaps more importantly, these regulations will effectively cause an expansion of the health gap that exists between high- and low-income Canadians. In section 1 terms, this style of regulation does not fail the 'minimal impairment test', but it seems to fail the last portion of the proportionality test outlined in *Oakes*. Proportionality is not struck "between the effects of the measures which are responsible for limiting the *Charter* right or freedom, and the objective which has been identified as being sufficiently important." (*R. v. Oakes*, p. 240) A full analysis of the section 1 test has not been warranted; the purpose here was not to determine how courts should attempt to resolve the issue of government regulation of professions in terms of cost-cutting. Rather, it served as a practical ethical analysis. This survey of data intended to illustrate the practical political realities that of cost-containment in Canada as well. Not only does it seem that the negative effects of the proposed measures outweigh the pressing objective addressed by the government, but the government's own objective – to close the health gap – also is thwarted by regulating physician billing numbers in urban areas.

Conclusion

Even though a constitutional right to practice one's profession does not exist, an examination of government attempts to restrict physician billing numbers in urban areas has indicated a basis for such a moral right, at least a limited one. A practical ethical analysis of this claim was conducted using section one of the *Charter* as background. Employment is an essential vehicle through which society allows a person to become a constructive member of that community, and one who contributes to the overall good. While not constitutionally protected, the government must have good reasons for disregarding this moral claim. Moreover rather than making the situation worse in other areas, the governments intended action should better it. As Dr. J. Armstrong, President of the Canadian Medical Association (1996), puts it: "The fiscal health of the nation should not be cured by detrimental changes to the health of Canadians."

Even though the government's fiscal austerity claims were examined, they may be only political spin. The economy of Canada has been steadily collapsing since the 1960s; every year, the total GDP per capita has declined. Thus, even though health expenditures have increased, the GDP has decreased. While this ratio (health $/GDP), has become larger, closer examination of the data indicated that Canada spends *less money per capita* than Japan on health care. Yet, Deber asserts that, "If we don't change soon we won't be able to sustain our system."[16] The issue now is appropriateness; what are the appropriate measures that government and the medical community take in order to make the healthcare system more efficient. 'Band-Aid' solutions to fee-for-service medicine are inappropriate when the system has 'cuts that needs stitches' and 'limbs that need amputation.' We need to look for other forms of health care delivery; capitation, integrated system delivery or other managed care models need to be examined for their appropriateness.

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Reference Re ss. 193 and 195.1(1)(c) *of the Criminal Code*[15] c (*Re: Motor Vehicle Reference*, [1985] 24 D.L.R., 548)

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In the Literature: The *UTMJ* Club

Andrew Lustig, BSc (0T0), and
Sean Wharton, BScPhm, PharmD (0T1)

This section of the New and Views will present updates of recent advances in the medical, and scientific literature. This section will also present critical appraisals of randomized control trials, systematic reviews and meta-analysis, in an attempt to develop an evidence based medicine focus. Future *UTMJ* issues will contain a user's guide to the application of evidence based medicine.

Nancy Olivieri Reveals Iron Chelating Drug Causes Toxicity

Deferiprone (L1) is an orally active iron chelating agent that, initially, revealed promise as a treatment for iron overload in thalassemia major patients. Treatment for thalassemia includes routine blood transfusions, which result in toxic iron deposits in organs, especially the liver. The current pharmacological therapy for iron overload is deferoxamine (Desferal), an iron chelator administered subcutaneously by an infusion pump. This procedure is painful and difficult to manage. Dr. Nancy Olivieri, at the Hospital for Sick Children (HSC), conducted clinical trials with deferiprone, comparing it to deferoxamine. Olivieri *et al.* demonstrated that prolonged treatment is associated with a decline in the drugs effectiveness. Liver biopsies, for 7 of the 18 patients treated for 4.6 years revealed toxic iron concentrations. It was found that 5/14 and 0/12 patients developed liver fibrosis in the deferiprone group and deferoxamine group respectively. Olivieri *et al.* report that deferiprone does not adequately control iron burden and may worsen hepatic fibrosis. These results have been challenged by Apotex Inc., the manufacturer of the deferiprone. See article in this issue for details of this ongoing controversy.

Source: Olivieri N. et al. (N Engl J Med 1998;339:417-423)

Lazarou Demonstrates that Adverse Drug Reactions may be Fourth Leading Cause of Death

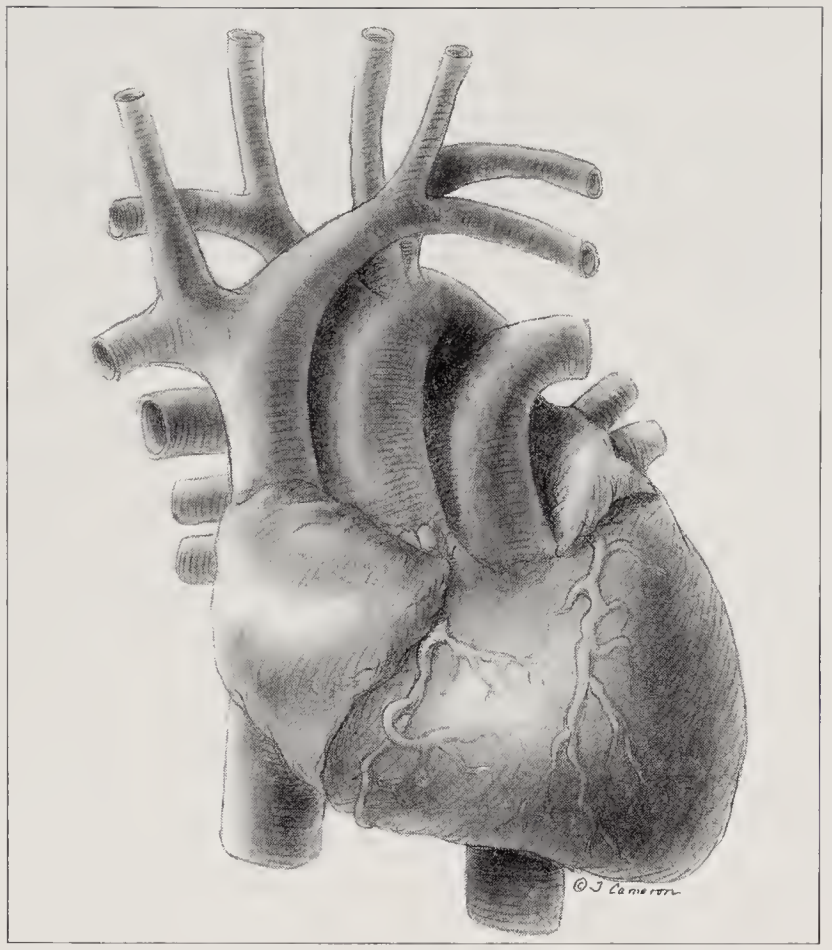
A recent meta-analysis published in *JAMA* estimated the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients. The study assessed 39 prospective studies that monitored all ADR occurrences for patients admitted to the hospital with an ADR, and those experiencing an ADR while in hospital. The overall incidence was 6.7% and 0.32% for serious ADRs and fatal ADRs respectively. The definition of ADR excluded therapeutic failure, overdoses, drug abuse, and errors in administration. These results are startling, as using conservative confidence intervals, ADR would rank ahead of pneumonia, and diabetes, as a leading cause of death. Meta-analysis' have limitations, mainly relating to the quality of the studies assessed. Heterogeneity (a statistical test assessing the degree of difference of study results) determined as significant suggests that study results should not be combined. In this meta-analysis the heterogeneity was significant ($p=0.009$, $p=0.04$), yet the major factors that differed were number of drug exposures per patient and length of hospital stay. Both of these factors can differ at each site due to patient population and are factors in ADR, and therefore are permissible. This meta-analysis had narrowly defined criteria which were improved compared to a previous study, and the results were conservatively reported emphasizing the degree of impact of these results. ADR are clearly an important clinical issue that needs to be addressed within health care.

Source: Lazarou J. et al. JAMA 1998;279(15):1200-1205.

Beta-Blockers Used in Congestive Heart Failure (Aren't they Contraindicated?)

All beta-blocker drug monographs clearly state that these agents are contraindicated in congestive heart failure (CHF). Beta-blockers decrease heart rate and are negative inotropic agents (decrease force of contraction). Negative inotropes can aggravate CHF leading to sudden death, yet beta-blockers (carvedilol, and metoprolol) are being used successfully to decrease mortality of CHF patients. When used at low doses (avoiding significant negative inotropic effects), beta-blockers can reduce the compensatory mechanisms (primarily high sympathetic tone) in CHF. This readjustment may allow the failed heart to repair and become resensitized to catecholamines. Two large studies have demonstrated that carvedilol (dose titrated up slowly) can decrease mortality, and a recent study (unpublished) with metoprolol was ended early because of a significant decrease in mortality. The magnitude of benefit is still unclear with these drugs, but recent evidence indicates a significant effect.

Source: Massie B Lancet (1998):352 (suppl 1):29-33



Teddy Cameron

Moderate Alcohol Consumption During Pregnancy - No Risk of Malformations

Fetal Alcohol Syndrome (FAS) is characterized by growth retardation, facial dysmorphology and central nervous system dysfunction. Major and minor malformations, spontaneous abortions and decreased birth weight have been among the many reported consequences of heavy alcohol. Half of the pregnancies in North America are unplanned, and many women, unknowingly, extend drinking into the first trimester of their pregnancy. The effects of heavy alcohol use are evident yet the effect of moderate alcohol consumption defined as two drinks per day, on fetal malformation was unclear until a recent meta-analysis. Seven studies, comprising 20,000 babies exposed to moderate alcohol, were assessed. The odds ratio (OR) for major malformations was 1.01 (CI, 0.94 - 1.08), indicating that there is no increased or decreased risk.. An OR of 1.00 signifies no risk, below 1.00 signifies a protective effect (typically below 0.05), above 1.00 represents an increased risk. The studies were not significant for heterogeneity, confirming that they can be combined. This study has numerous limitations due to inaccurate self reporting of alcohol use, a lack of defined alcohol content, and inconsistent definitions of malformations. This study does not attempt to justify drinking during pregnancy, instead it should decrease anxiety and prevent false alarms leading women to consider termination of otherwise-wanted pregnancies.

Source: Polygenis et al. (1998) Neurotoxicology and Teratology. 20(1):61-67.

Chewing Gum Prevents Ear infections

Xylitol, a commonly used sweetener, often used in chewing gum, is effective in preventing dental cavities. As it inhibits the growth of pneumococci, a recent study evaluated whether xylitol could be effective in preventing acute otitis media (AOM). 857 healthy children were recruited from day care centers and randomized to one of five treatment groups to receive control syrup, xylitol syrup, control chewing gum, xylitol gum, or xylitol lozenge. The design was a 3 month, double blind, RCT. AOM was experienced in 41% of the control syrup group, and only in 29% of the xylitol syrup group, resulting in a 30% decrease. Likewise, there was a 40% decrease in the xylitol chewing gum group and a 20% decrease in the lozenge group. Xylitol was well tolerated. The children on Xylitol required antimicrobials less often than did controls. Xylitol sugar, when given in a syrup or chewing gum, was effective in preventing AOM and decreasing the need for antimicrobials. Questions remain regarding the duration of therapy, whether the agent can abort, or treat infections and the minimum effective dose. Further studies are needed to confirm this data, and use in children with chronic AOM should be assessed.

Source: Matti U et al. (1998) Pediatrics 102:879-884 (October)

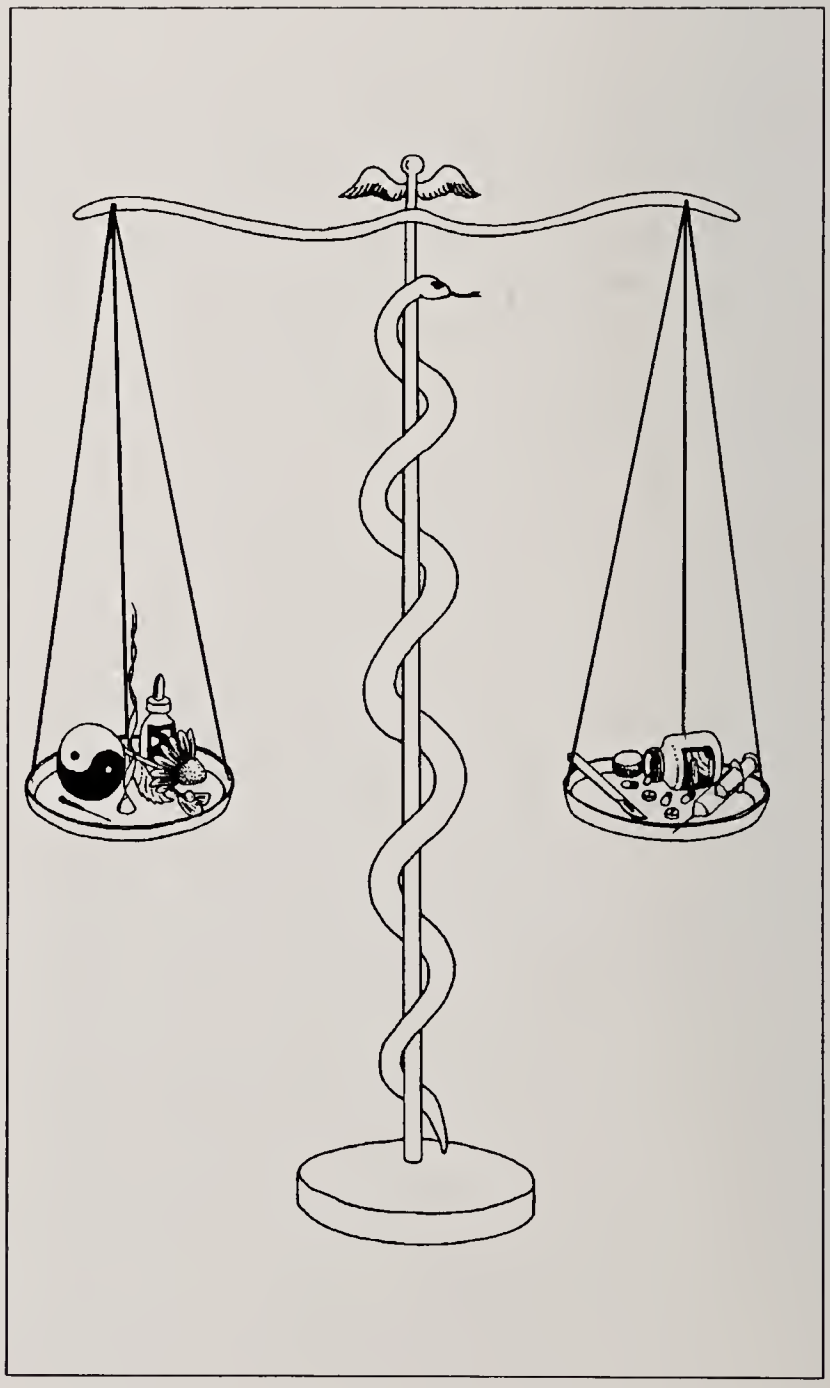
UTMJ Series on Complementary and Alternative Medicine (CAM)

Part 1: Introduction

Ryan Margau, BSc., and Sean Wharton, BSc.Phm, PharmD

Complementary and Alternative Medicine (CAM) is a growing and controversial field within health care. This article is the first of a three part series on CAM appearing in the *UTMJ*. This commentary defines CAM and explains why physicians, and other conventional health care providers, must have knowledge about this topic. Subsequent sections of this series will focus on various aspects of alternative treatment.

It is vital for Canadian physicians to have an awareness of CAM. As a group, complementary and alternative health care providers practice non-allopathic,[a] or unconventional medicine (Figure 1). A possible definition of CAM, proposed by Eisenberg *et al.* is that it involves perceptions of illness and therapy not officially taught in traditional Western medical institutions.[1] There are many unanswered questions surrounding the validity and effectiveness of the spectrum of unconventional therapies. In spite of this, there is increasing use of these treatments among Canadians.[2-6] The reasons underlying the growth of this field have far reaching implications for conventional physicians.[7] Moreover, additional controversy surrounds the educational, licensing and regulatory standards for CAM practitioners. Consequently, the College of Physicians and Surgeons of Ontario (CPSO) has adopted guidelines on how doctors should deal with CAM.[8] This is a step in the right direction, increasing coordination between allopathic and non-allopathic professionals to provide safe and sufficient health care.



Jacqui Shaw

a There is no official definition of the term non-allopathic medicine. What is condered alternative medicine in the Western world is officially accepted and recognized as standard practice in other parts of the globe, such as China and India.

The presence, or lack of, scientific evidence substantiating alternative medicine is subject to wide debate. While complete analysis of this issue is beyond the scope of this introduction, it is worthwhile to note that the National Institute of Health (NIH) in the US has recently been granted the budget to study CAM in greater detail.[9] Such studies should provide scientific results regarding the efficacy of CAM treatments. Notwithstanding these developments, the increasing use of non-allopathic treatments by Canadians cannot be ignored. The most recent scientific study, The National Population Health Survey (1994), concluded that 15% of Canadians aged 15 and over (3.3 million people) used alternative practitioners other than chiropractors in 1993.[b] Further data from Statistics Canada estimates that Canadians paid in excess of $1 billion in 1996 for chiropractic, naturopathic, homeopathic and herbal therapies not covered by health plans, with an annual growth rate of 20 per cent.[5,6] Physicians and other conventional health care providers can not ignore the fact that so many Canadians are turning to alternative medicines.

The reasons behind trends towards unconventional treatments are complex. Explanations for this phenomenon point to problems within the health care system that have a direct impact on physicians. Patients have rebelled against a health care system they perceive as impersonal and mechanistic.[4,7] Disenchantment with conventional medicine has favored development of non-allopathic remedial treatments. An acute example of this phenomenon is that at least 80% of cancer patients use some form of alternative therapy,[10] potentially due to feelings of hopelessness and disparity. Other reasons cited for turning to alternative medicine include: beliefs that treatments are harmless and may help, failure of regular medication, intolerable side effects from conventional therapy, emphasis on treating the whole person and increased patient autonomy.[3] Such findings highlight potential flaws within Western medicine. Moreover, criticism against conventional medicine damages the integrity of allopathic health care professions. These issues should be addressed since they effect all physicians.

Another important aspect of CAM is the lack of uniform educational, licensing and regulatory standards. Only some areas of CAM, such as Naturopathic Medicine (Figure 1), are subject to extensive educational and licensing requirements.[2] Naturopathic medicine grew out of alternative healing systems first appearing in 18th and 19th century Europe.[11] Naturopathic Doctors (NDs) practice treatment modalities including: acupuncture, herbal medicine, homeopathy, naturopathic manipulation, hydrotherapy, clinical nutrition and lifestyle counselling.[9] NDs receive their education from American colleges or through a four year program offered by the Canadian College of Naturopathic Medicine (CCNM), and must pass a scientific and clinical Naturopathic Physicians Licensing Exam (NPLEX).[9] In Canada naturopathic practitioners are currently licensed in British Columbia, Saskatchewan, Manitoba and Ontario.[2,c] Ontario licensing falls under the Drugless Practitioners Act of 1925; however, the profession is currently seeking recognition under the Regulated Health Professions Act similar to other conventional provincial health professionals.[2] NDs can be contrasted with other CAM providers (reflexologists, independents acupuncturists and herbalists etc.) that do not have licensing bodies holding them accountable for inappropriate practice.[6]

Homeopathic and herbal remedies are available without a prescription; they are not subject to the same regulations as prescription drugs.[12] The purity and content of active ingredients may be questionable, and consumers have little protection against side effects or financial loss.[12]

The growing use of alternative medicine, the reasons underlying this trend and the problems posed by insufficient regulation, are sparking physician interest in CAM. This interest is in keeping with the extensive media hype on the topic. The College of Physicians and Surgeons of Ontario has adopted guidelines regarding alternative therapies. The 1997 report to council of the Ad Hoc Committee on Complementary Medicine set recommendations for physicians practicing, or giving referrals for CAM.[8] The committee recommended that physicians employ conventional diagnostic measures at all times. Further recommendations state that physicians must first inform patients about conventional treatments, and indicate that alternative therapy is outside the scope of normal practice.[8] The CPSO also asserted that CAM must not, need not, and should not be unduly limited by scientific reductionism, while recognizing that all therapies should be safe and cause no harm.[8] The CPSO position indicates that alternative practice has been recognized by the medical community, although specifics on monitoring and standards are at early stages of development.

This policy places Ontario among the leaders in recognizing the increased use of CAM, yet implies that physicians have knowledge about the extent of proven treatment efficacy. Physicians commonly encounter patients using widely publicized alternative therapies such as ginseng, echinacea and acupuncture. An understanding of these topics is important

b This study involved 17,629 respondents from all regions and income categories constituting a recent and reliable source of statistical information. Alternative practitioners were defined as: naturopathic doctors, massage therapists, homeopaths, acupuncturists, herbalists, relaxation/biofeedback teachers, reflexologists or spiritual healers.[2]

c The enrollment at the CCNM has skyrocketed over the past few years to the current level of 400 students annually.[9] By the year 2003 Canada will have over 1000 licensed NDs, double the current figure.[9]

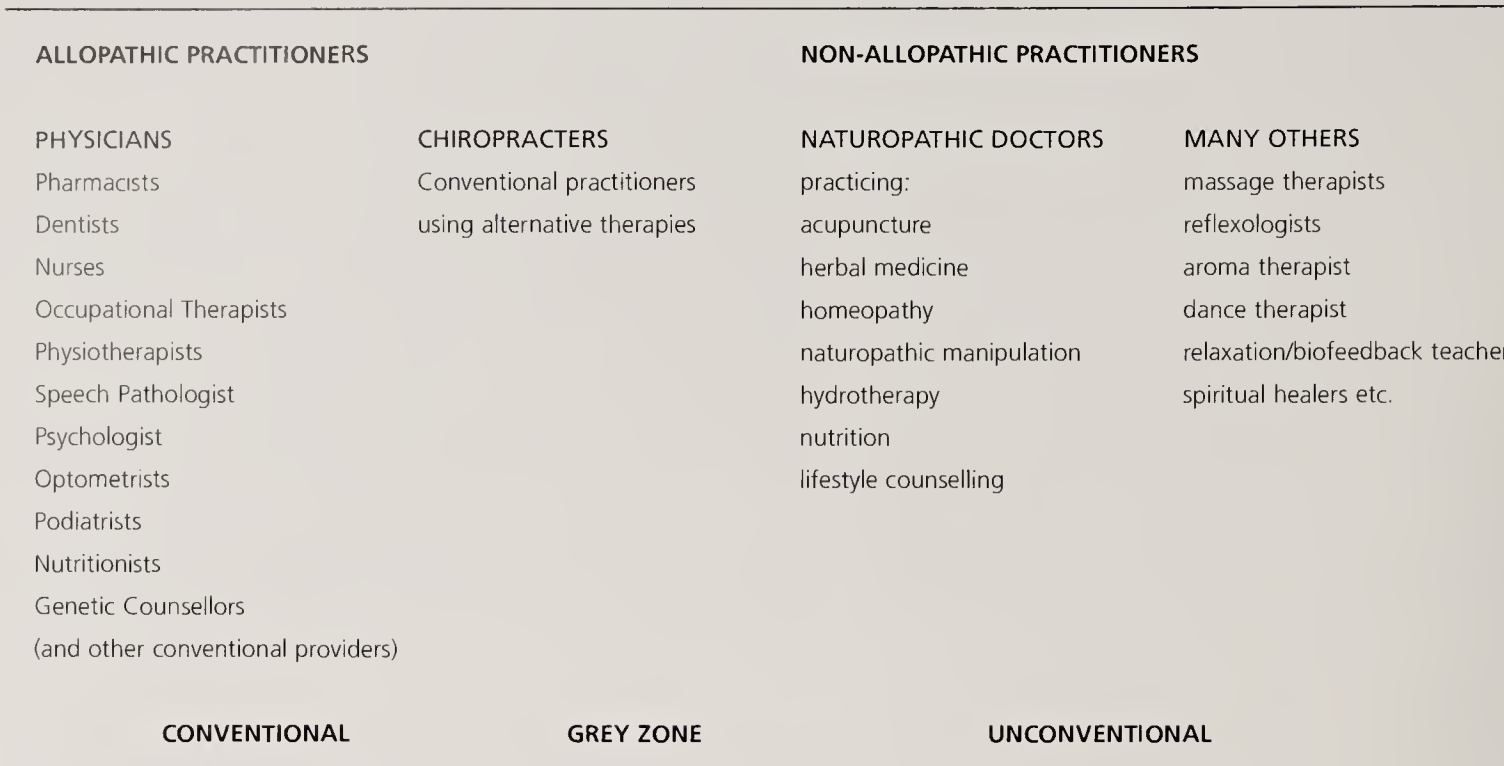


Figure 1. *Schematic Classification of Health Care Providers.*

as it enables effective patient counseling. The comments by Dr. Kazimirski at the 1996 Canadian Symposium on Alternative Medicine summarizes the position practitioners should have to all therapies. She reminded physicians that regardless of the type of medicine patients choose, they should have the right to expect that it has been proven safe.[10]

Through this series the *UTMJ* hopes to spark interest in, and learning about, Complementary and Alternative Medicine. The debates surrounding the scientific merit of CAM therapies, and the inconsistencies in educational, regulatory and licensing standards for CAM practitioners are serious issues. Despite these uncertainties, the use of alternative medicine is becoming increasingly prevalent. The reasons behind this occurrence may indicate conventional medicine's failure in meeting the needs of those using CAM. Clearly, unconventional medicine is a topic that should not be ignored. With continued direction from our provincial and national associations, licensure of alternative practices and governmental monitoring of alternative products, allopathic medicine and CAM may eventually complement each other. This would ensure safe and effective health care for all patients.

Acknowledgement

The authors would like to acknowledge the assistance of Heather Boon, BScPhm, PhD, Faculty of Pharmacy, University of Toronto. Dr. Boon researches the practice of complementary and alternative medicine and its application to allopathic health care.

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The Corporate Take Over of Academic Research: The Nancy Olivieri Story

Stella Yiu, B.Sc. (0T1)

For the past few months, there have been several events that highlight the increasingly uneasy partnerships between industry and clinical investigators. Dr. Betty Dong, at The University of California, was sued by Boots Pharmaceuticals for publishing a study suggesting that other generic thyroid products were bioequivalent to the one manufactured by Boots.[1,2] Dr. David Kern at Brown University was sued by Microfibers Inc. for disclosing occupational hazards to its employees.[3] In Canada, the conflict between Dr. Nancy Olivieri, a senior researcher at the Hospital For Sick Children, and the pharmaceutical company Apotex Inc. has been prominently featured in the headlines. The following article is based on a conversation with Dr. Nancy Olivieri regarding the events surrounding this Canadian based controversy. Any commentary does not necessarily represent the views of the editors or contributors to the *UTMJ*.

The Players

Dr. Nancy Olivieri
- Director of the Hemoglobinopathies at the Hospital For Sick Children (HSC) and the Toronto General Hospital
- Professor, of the Department of Medicine and Pediatrics at University of Toronto
- Internationally renowned researcher in thalassemia and sickle cell disease

The Study
- A multi-centered, randomized controlled study comparing the efficacy of L1 (deferiprone) versus Desferal (deferoxamine) on lowering hepatic iron concentrations in transfused thalassemic patients

Apotex Pharmaceutical Inc
- A Canadian pharmaceutical company, primarily manufacturing of generic drugs
- Currently developing into a pharmaceutical firm that conducts original research leading to the licensing of parent drugs
- Markets the drug L1 (deferiprone) in Canada

Hospital For Sick Children
- World renowned research centre in pediatric medicine

Dr. Michael Spino
- Senior Vice-President of science affairs at Apotex
- Professor of Pharmacy, University of Toronto

Others
- Several prominent physicians and researches from Toronto and abroad have written letters of support on behalf of Dr. Olivieri

As a group, the thalassemias are among the most common genetic disorders in the world. The thalassemias are part of the group of disorders known as the hemoglobinopathies. These diseases represent a major health burden; about 100,000 babies worldwide are born with severe forms of the disease each year. Patients have defects in hemoglobin production and function, resulting in severe anemia, splenomegaly and enlargement of cranial and facial bones. Researchers are actively conducting clinical research on the design, effectiveness, efficacy, complications, compliance and other aspects of treatment.

Treatment for thalassemia includes routine blood transfusions. However, frequent transfusions can cause iron overload in multiple organs, leading to cirrhosis, diabetes mellitus, adrenal insufficiency and failure to mature sexually. For the past 25 years, patients have been treated with deferoxamine (Desferal), an iron chelator which minimizes iron deposition. Desferal is administered subcutaneously by an infusion pump for 12 hrs for 4-7 days a week. Many patients find the routine cumbersome, painful, and difficult to manage, leading to significant non-compliance. As a result, serum iron levels can become toxic.

A few studies have suggested that L1 (deferiprone), an

experimental oral iron chelating compound might be able to decrease iron levels in transfused patients. As an oral compound, L1 would have significant compliance and administration advantages over Desferal, which is administered subcutaneously. In 1989 at the Hospital for Sick Children(HSC), Dr. Nancy Olivieri began clinical trials with L1. Apotex, who market the drug in Canada, offered to partly finance the multi-centred study. Apotex contributed $120,000 a year for 2 1/2 years to the HSC study. The Medical Research Council (MRC) of Canada also financed the trial. In addition, Dr. Olivieri signed a confidentiality agreement, which stipulated that the data obtained from the study would require approval by Apotex prior to publication. This study was designed to measure the effectiveness of L1 relative to Desferal by measuring liver iron levels in study participants. An effective chelating agent should produce very low liver iron levels and therefore decreased liver fibrosis.

By late 1995 the liver biopsies from some of the study participants in Toronto that were receiving L1 revealed increased iron levels with resultant liver fibrosis. This lead Dr. Olivieri to suspect that, at least in some patients, L1 was ineffective. However, Dr. Olivieri did believe that the drug might still be useful in treating some patients, whose hepatic iron concentrations had not risen dangerously. Dr. Olivieri believed that the study should continue to determine which patients would benefit from the new drug. However, she also believed that all patients must be told of the new findings, and the possible risk they faced if they continued taking the drug. Dr. Olivieri suggested that the patient consent form be changed to reflect the new findings. The previous patient consent forms primarily discussed the initial success of L1, excluding toxicity information.

Dr. Olivieri and her American colleague, Dr. Gary Brittenham of Columbia University, informed Dr. Michael Spino, senior vice-president of science affairs at Apotex, about their concerns about L1's ineffectiveness. Dr. Spino did not agree that the patients were at risk. He also did not acknowledge the need to revise the patient consent forms. Dr. Spino noted that Dr. Olivieri had not presented sufficient evidence to show the drug's potential ineffectiveness and resultant toxicity. He saw no cause for alarm, stating that researchers at the two other sites studying L1 (Philadelphia and Italy) had not observed any toxicities, although their patients had not been taking the drug as long as the Toronto patients. Furthermore, Apotex was concerned that Dr. Olivieri's actions could jeopardize the chances of the drug's being approved by government regulatory agencies.

The drug trial continued. Still concerned about the safety of L1, Dr. Olivieri then approached the HSC ethics board, where it was concluded that the patients must be informed of the potential risks of the drug L1. She drafted a new patient consent form that would inform patients of the risk if they continued in the study. This form was presented to Apotex.

On 24 May 1996, Dr. Olivieri was immediately discharged as the chairperson of the study's steering committee by Apotex. 72 hours later, Apotex staff arrived at the hospital and removed all L1 from the pharmacy shelves, stopping the Toronto study prematurely. Dr. Olivieri was threatened with 'full legal remedies' if she informed the patients, or published her data and findings. Even though the study was halted in Toronto, about 600 patients in Italy and Philadelphia were still taking L1.

Two months after discontinuing the trial at the HSC site, Dr. Spino noted that Apotex took Dr. Olivieri's concerns seriously and had assembled a review by a panel of experts to examine her results. This expert panel concluded that L1 was effective and the trial should continue at the other sites. How the same set of scientific data could produce such opposite conclusions is still unknown. One panel member has suggested that Apotex may not have provided her with all the available data. However, it was apparent that concerns about L1 were growing. One month after the panel meeting, a second panel member published data in L1 treated patients confirming Dr. Olivieri's concerns.

Apotex threatened to take legal action against Dr. Olivieri in the event that she informed study participants in the HSC trial of the drug's toxicity, or if she published her findings. Despite these threats Dr. Olivieri alerted patients, their parents, and drug regulatory officials in Ottawa and Washington. Furthermore, Dr. Olivieri published her finding regarding the potential L1 toxicity as the lead article in the August 13th issue of the *New England Journal of Medicine*.[6] Dr. Olivieri has also presented her findings at international scientific meetings. Dr. Spino has attended several of these conferences and presented contrary findings. Dr. Olivieri requested the HSC administration hire a lawyer on her behalf as the threats of legal action continued. Her request was denied.

HSC physicians and scientists have criticized the hospital's neutrality, claiming that such silence will foster suspicion of the hospital being solely supportive of Apotex, which provides research funds to HSC each year. Dr. Olivieri's supporters also claim that she did not receive adequate support from the University of Toronto. Recently, the University of Toronto revealed that the university will be receiving a 20 to 30 million dollar donation from Apotex.

HSC scientists and researchers have recognized that Dr. Olivieri acted correctly by speaking out against Apotex and acted in the patient's best interest. However, attempts to secure appropriate support from the hospital and the university were unproductive. Since early 1998, 140 physicians and researchers have signed a petition demanding that the hospital administration hold an external inquiry to address the issue of contracts with researchers and pharmaceutical companies. An external inquiry would involve the assessment of a research contract by a neutral third party, i.e. a reviewer that is external and independent of any and all of the parties involved in the case. An external inquiry may determine what considerations should be made in the future to ensure that a

similar situation does not occur. In light of the increasing dependence of research on industry money, researchers at HSC are concerned that what has happened to Dr. Olivieri could happen again. Such funding could lead to problems if safeguards are not in place to protect academic freedoms, such as the right to publish results regardless of the consequences to the private companies.

Initially, HSC decided that it would only conduct an internal review on its policies and procedures, rather than an independent external inquiry. The hospital refused to examine the details of the Apotex affair. Some top researchers, including Dr. Brenda Gallie, Director of Blood and Cancer Research, indicated how difficult it would be to continue research productivity if an external inquiry was not conducted, as researchers would be working under the threat of a possible recurrence of the Apotex/Olivieri situation. Dr. Olivieri and her supporters feel that there is a duty for the hospital and scientists to protect patients during research studies. According to the Declaration of Helsinki, the research mandate is to prove that a treatment is safe. If there is any indication that a treatment is unsafe, all attempts should be made to return to original animal trials to determine toxicity, or to conduct human trials with patients who have knowledge of the potential toxicity and are willing to take the risk. Research into toxicity levels should not continue in uninformed patients. Assessing known toxicity in humans is similar to continuing to use thalidomide in pregnancy to determine which malformations will occur. Researcher at HSC would like an external inquiry conducted that would address these issues and would result in recommendations to protect the freedom of researchers and reassure public trust in HSC.

As a result of the continued pressure from the HSC researchers, the HSC board of trustees agreed to an external inquiry in October 1998. Dr. Arnold Naimark, a former vice-chancellor of the University of Manitoba and the current director of its Centre for the Advancement of Medicine, was selected to conduct the review. Dr. Olivieri and her supporters initially welcomed the review, but later refused to participate because they disagreed with the manner in which the reviewer was chosen. Researchers at HSC had hoped that a panel of reviewers would be chosen. Instead a single reviewer was obtained. The reviewer was chosen unilaterally by the hospital administration without any input from the other parties involved. Researchers at HSC were also concerned that Dr. Naimark has a potential conflict of interest in conducting the review. During his term as the vice-chancellor of the University of Manitoba, the school received research funds from Apotex. The group's suggestion of another individual to join the review panel was refused. The board of trustees insisted on Dr. Naimark's objectivity, saying that Dr. Naimark will complete the review by November 30,1998 with or without the participation of Dr. Olivieri and her supporters. In the October 1998 issue of the HSC newsletter, Dr. Naimark remarked that his report will be more than just mere facts, but will include lessons to be learned and an evaluation of the issues and challenges that HSC should deal with. However, Dr. Naimark will primarily establish a chronology of events and issues, without any assignment of responsibility and accountability. Recently, the hospital has agreed to include two other reviewers who will be chosen from a list put forth by both parties. This 'inquiry' was mandated to determine facts and circumstances of the controversy.

This debate will continue. Researchers, clinicians and medical students will follow this story as it unfolds. These discussions may eventually produce recommendations that will support the preservation of the freedom to publish. It is imperative that a precedent be established to ensure that researchers around the world can conduct their work openly without fear of mandates from private sponsors. The freedom to publish must be protected.

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International Researchers May Now be in Line for Nobel Prize: The Gairdner Awards Recipients

Karol Wroblewski, BSc.

Every year since 1959 Gairdner Award has been presented to individuals who:

"... through unselfish devotion of their time and effort, have been successful in making major contributions through research in the conquest of disease and human suffering..."

James Gairdner, 1957

Forty nine of the awardees have later received the Nobel Prize. This year's recipients of this leading international award in biomedical science are Dr. Giuseppe Attardi, Dr. Elizabeth Blackburn, Dr. Carol Greider, Dr. Walter Neupert, and Dr. Gottfried Schatz.

In 1999, The Gairdner Foundation will celebrate its 40th Anniversary and will hold a major international symposium Oct 19-22 in Toronto involving at least 25 Gairdner Foundation Awardees. Mini-symposiums will also be held outside of Toronto in Vancouver on Oct 18-19, 1999 and Montreal on October 19, 1999.

Acknowledgements

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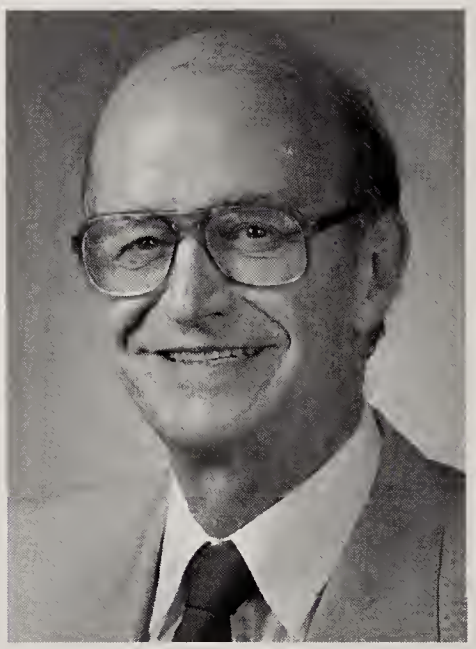
Giuseppe Attardi, MD



Dr. Attardi was born in Sicily, Italy. He obtained his MD degree at the University of Padua. He received graduate training from the Karolinska Institute of Technology in Stockholm and Washington University in St. Louis. Since 1963 he has been associated with the California Institute of Technology at Pasadena, where he is currently a professor of Molecular Biology in the Division of Biology. Dr. Attardi has been awarded the Antonio Feltrinelli International Prize for Medicine. He became a Guggenheim Fellow in 1970 and 1986, and he is a member of the National Academy of Sciences.

Dr. Attardi is recognized for his contribution to the understanding of the structure of human mitochondrial genome and its role in disease. His work includes description of the genome and the demonstration of the presence of functional genes in it. Dr. Attardi has been analyzing the nature of mutations in these genes and their effect on cells. He also initialized documentation of changes in mitochondrial genome during the course of human life with implication for aging and cellular senescence.

Elizabeth Blackburn, BSc., MSc., Ph.D and Carol Greider, Ph.D

Dr. Elizabeth Blackburn and Dr. Carol Greider are jointly recognized for the discovery of the structure of telomeres and the enzyme telomerase. By maintaining the length of telomeres telomerase prevents the damage of chromosome ends which would occur as a result of chromosome duplication. Understanding of the changes that occur in the structure of telomeres might provide insights into the aging process of body cells as well as into the process of immortalization of cancerous cells.

Dr. Blackburn has begun her scientific career at the University of Melbourne, where she received her BSc. and MSc. She received her Ph.D in 1975 from the University of Cambridge, UK. In 1987 Dr. Blackburn joined the Department of Molecular Biology at the University of California in San Francisco where she is presently a professor of Microbiology and Immunology, and Biochemistry and Biophysics. Dr. Blackburn is a member of the National Academy of Sciences, and a Fellow of the Royal Society. She is a winner of the NASc Award in Molecular Biology, and a recipient of the Australian Prize in 1998.

Dr. Carol Greider is an Associate Professor in the Department of Molecular Biology and Genetics at John Hopkins University School of Medicine. She received her Ph.D in 1987 from the University of California at Berkeley, where she worked in Dr. E. Blackburn's laboratory. For several years she was a researcher at Cold Springs Harbor Laboratory. In 1996 Dr. Greider was appointed to the National Bioethics Advisory Commission. She was the winner of the Schering-Plough Scientific Achievement Award in 1997 and the Cornelius Rhodes Award in 1996.

Walter Neupert, MD, Ph.D and Gottfried Schatz, Ph.D

Dr. Walter Neupert and Dr. Gottfried Schatz were awarded "for their discovery of the transport of proteins into the mitochondria." This process has implications for diseases that result from mitochondrial defects and which affect muscle and brain. Dr. Neupart and Dr. Schatz discovered that the presence of specific sequences in cytosolic proteins is necessary to direct them to mitochondria and that a mitochondrial channel is formed to take up these proteins.

Dr. Neupert received his MD and Ph.D from the University of Munich, where currently he is a professor of Biochemistry and Cell Biology. His research work includes various problems of mitochondrial biogenesis, mitochondrial protein folding, assembly, and degradation, as well as the movement of mitochondria within cells. Author of over 240 papers, Dr. Neupart is on the editorial board of the European Journal of Cell Biology and is Monitoring Editor of the Journal of Cell Biology. He served as a president of the German Biochemical Society and is currently the Chairman of the EMBO Council. Dr. Neupart's honors include the Heinrich-Wieland Prize in 1993, the Feldberg Foundation Prize in 1996, and Academia Europaea.

Dr. Schatz received his Ph.D in Chemistry and Biochemistry from the University of Gratz, Austria. Since 1974 he has been a professor at the Biozentrum of the University of Basel, Switzerland. Dr. Schatz served as a Secretary General of the European Molecular Biology Organization (EMBO). Author of more than 180 papers, he received more than a dozen international prizes and was elected to the U.S. National Academy of Sciences. *(See Interview, p.36).*

The Future of Biological Science: An Interview with Gottfried Schatz, Ph.D

Interviewed by: George Thanassoulis, BSc.
Edited by: Karol Wroblewski, BSc.

This fall Dr. Gottfried Schatz visited Toronto to receive the prestigious 1998 Gairdner Award. *UTMJ's* George Thannassoulis interviewed Dr. Schatz who revealed how he became a leading mitochondria researcher and shared his views about the future of biological science.

UTMJ: How did you become a researcher and what influenced you to study mitochondria?

Gottfried Schatz: I started off being very interested in chemistry. As a teenager I spent virtually all my allowance running a little chemical laboratory from our three room apartment to the horror of my parents. It was very clear that I would want to study chemistry which I did and finished. But towards the end it was clear that there were some things that I could not explain as a chemist. This was mainly the living matter. At that time, almost forty years ago, there was still the question whether there were certain laws that only applied to living things but not the non-living world. I thought this was sufficiently interesting to switch to biology. My choice to investigate mitochondria was almost accidental. After finishing my Ph.D. I wrote nice post-cards of my town to all the people whose work I liked from library readings. Not knowing what a reprint request card was, I used the post-cards and asked these people to send me all their reprints. Obviously most people did not reply to such nonsense, but one person did and sent me all his reprints. It was a huge package that came air freight. It must have cost a fortune. This person was David Green, a very famous American scientist who was working on mitochondria. I found his work so fascinating that I said "I'm going to do it".

UTMJ: Few people are aware of the fact that you were the first person to demonstrate that there is DNA in mitochondria. Can you comment on this?

Schatz: Indeed, this is a secret I have. It was the first thing I did. Actually, there were two labs which found the same thing: our lab in Vienna, and another lab in the U.S. Most people have forgotten in fact. I have gotten many prizes in my career - all of them for other things. Of course, at that time this finding seemed completely unimportant. It took thirty years for this thing to become as explosive an issue as it is today. Today, we know that mitochondrial DNA is important in medicine, forensics, and in retracing human history.

UTMJ: Currently, you are working on translocation of proteins into the mitochondria. Why are you interested in this process and where do you see this field going in the future?

Schatz: I want to understand how the mitochondria are put together in terms of proteins and how the proteins find their correct place on and in the mitochondria. For where the field is going, I think that the mitochondria have been viewed for a long time as a separate machine that sits in our

cells and makes ATP. Of course now we have seen that the barrier has been broken. Suddenly the mitochondria are now involved in a lot of cellular processes. The future will be to integrate the mitochondria with the rest of the cell function. So the cell biology as opposed to the biochemistry is only starting. This integrative approach is very true for many other lines.

UTMJ: In your opinion, which area do you see the biggest scientific discoveries being made in the future?

Schatz: By definition I cannot answer this question, because if I could, those discoveries would not be very surprising and therefore would not be good discoveries. But of course students always ask this question and for a good reason. It is very clear that the major advances during the next few years will come on two opposing fronts. On the one hand, on ever more complex systems. Developmental biology is clearly a field where we have many surprises waiting. Also, down the road, at the end of course: the human brain. This is the last frontier. Although we are very close to it, we still do not even know all the principles by which consciousness arises. On the other hand, going in the direction to ever simpler systems, like for example how the protein folds. Here we are waiting for smart ideas, but also for very powerful biocomputing and algorithms which are not yet available. So the major things will happen with the very small and the very big. But discoveries will also be made in the middle, in disciplines like medicine and metabolism for example. You have all learned the Kreb's cycle. I teach it to my students, but it is partly wrong. Now you do a knockout in a mouse and the phenotype is completely different than what the basic text will tell you. We see that there are networks now. So we are really only seeing the tip of the iceberg. Much of what you are taught is wrong, I just do not know what exactly...

UTMJ: It is interesting that you have mentioned developmental biology and brain, because many science historians have said that these may indeed be the last two frontiers of modern science. It has been proposed that once these two areas are conquered, science as we know it will be over, and that sorting out the details will be the only remaining work. Can you comment on this?

Schatz: This has been said many times before and it is of course always wrong because we really know very little about nature. How old is modern science? A couple of hundred years at the most. I believe we are the beginning. What forces drive evolution? We always assume that it is this blind mutation followed by selection. This was formulated a long time ago. Are we sure this is really true? The most important question for me is not how does the brain work. The most important question is where do we come from? How did life arise? The first question will be answered by going back to the past molecularly and finding out where we come from. The second question will be answered by understanding evolution better. I think these are really the fundamental questions. So I believe that in biology we are still essentially at the beginning of science. I also believe this is true for most of the natural sciences. "The end of science" has been proclaimed many times. However, historians know very little about science and this is one of the great intellectual catastrophes. It is unfortunate that the humanists have no idea what we do and actually dislike what we do. I believe that scientists know much more about the humanities than vice-versa. And the gap is widening all the time.

UTMJ: If you were to give advice to someone who is starting in science what would it be?

Schatz: Follow you heart. Listen to advice, but follow your instinct. The idea of which field may be the best, which profession might be the best should always be ignored. Practical things, like what university to go to if you want to do certain things. This is helpful. However, to decide what lab you should go to, just follow your heart. It is the same as getting married. There is some useful advice, but by and large you have to marry someone you like. That is when it is going to work the best. I wish more parents would think of this. I see so often as an educator so much go wrong when parents try to tell their kids what to do.

UTMJ: Finally Dr. Schatz, if you could do it all over again, would you do it the same way?

Schatz: Of course not. I would be terribly facetious if I would. I used to be in a different profession. I was a musician for many years. I think my ideal profession still is to be a really good conductor. This I would really like. But short of that, since I do not have time for that, science is hard to beat.

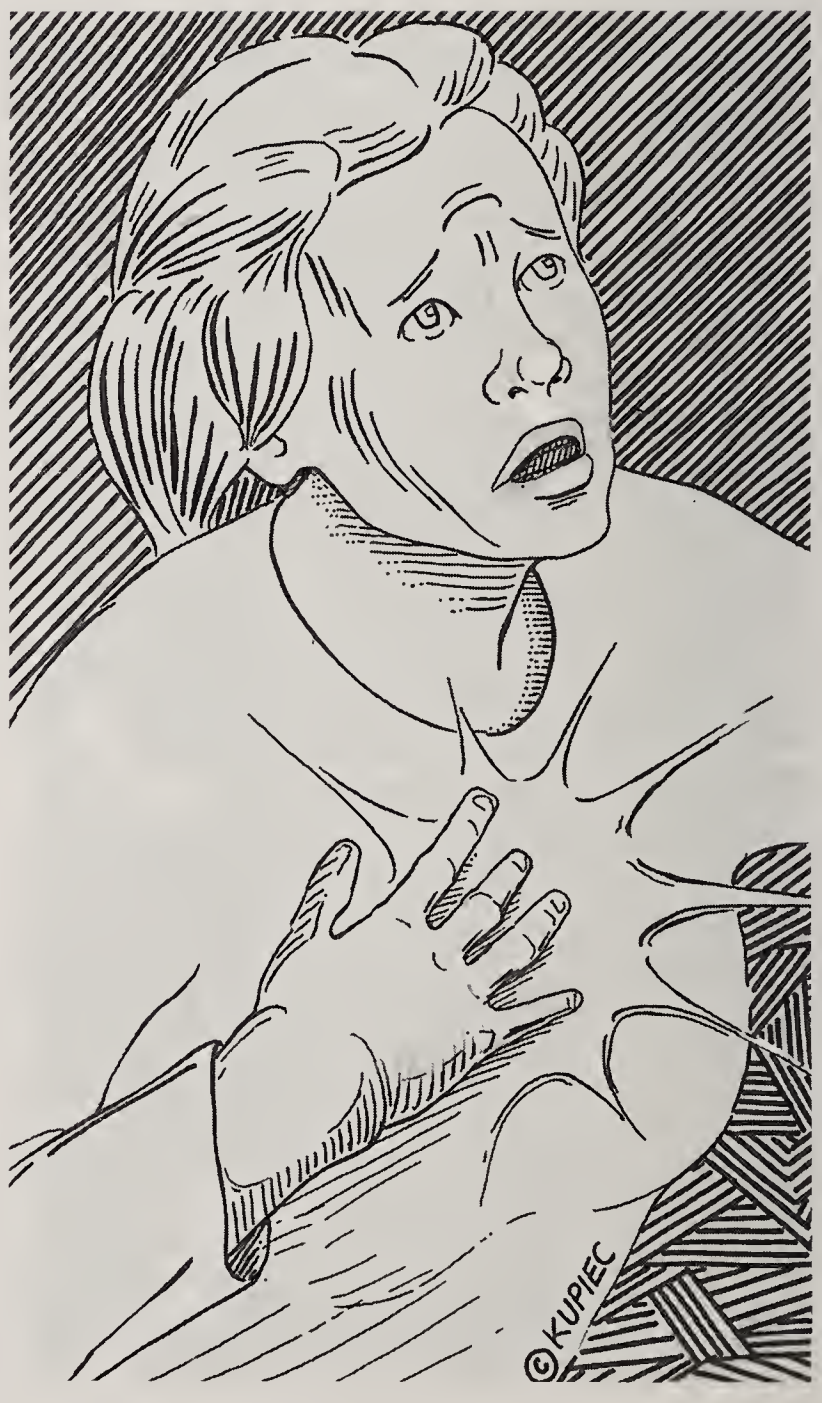
The Heart of the Matter

Mark Benaroia, BSc. (0T1), Ra Han, BSc. (0T0), and
Moira K. Kapral, MD, FRCPC, MSc.*

Introducing Morning Report

Morning Report Rounds are daily exercises that act as a learning tool for students and faculty in teaching hospitals throughout North America. The specific format of morning report varies amongst institutions, but typically involves the presentation of a clinical case, followed by a case-oriented discussion. At the University of Toronto, the informal goals of morning report are to facilitate teaching at various levels of medical training, to assess quality assurance with respect to medical treatment, and to discuss hospital structures that may hinder efficient and effective treatment. Ordinarily, the medical team (composed of medical students and residents) on-call the night prior to morning report, will present a clinical case from the previous day's admissions. A staff physician will then emphasize various components of the clinical reasoning process: generation of differential diagnoses; how to refine a diagnosis given additional information; anticipating laboratory findings; and preliminary discussions on patient treatment and management. This year the Editors changed the format of the Morning Report section from a discussion between a single presenter and physician to a coordinated collaborative discussion between medical students, residents, and a staff physician.

Please direct any questions or comments about the case to the editors at the following email addresses: m.benaroia@utoronto.ca and ra.han@utoronto.ca. We invite any clinician who has a case of educational value and who is interested in contributing to the *UTMJ* to contact the editors at the same email addresses above.



Nadav Kupiec

* Assistant Professor at the University of Toronto, and is in the Division of General Internal Medicine and Clinical Epidemiology at The Toronto Hospital

The Scene

A conference room in a Toronto teaching hospital. Students, residents and staff physicians are seated around a large table. Imran, a fourth year medical student, Reena, a first year resident (PGY-1), and Alice, a second year resident (PGY-2), have worked overnight, admitting patients to the hospital. They have selected one case from the previous night's admissions, which Imran will now present to the group. A faculty member, Dr. Thompson, will facilitate a discussion of the case.

Imran: This is a 65-year-old woman who presented to the emergency department with a chief complaint of chest pain.

Dr. Thompson: Let's pause here for a moment. Clinicians generally begin to form a differential diagnosis after hearing the chief complaint. Reena, when you hear this story of chest pain, what diagnoses do you consider?

Reena: The differential diagnosis for chest pain can be approached using the broad categories of *cardiac disease, pulmonary disease, gastrointestinal disease*, and *musculoskeletal disease*. Cardiac causes of chest pain include angina, myocardial infarction, pericarditis, and aortic dissection. *Pulmonary* causes of chest pain include pulmonary embolism, pneumonia, pleuritis, pneumothorax and tumours. *Gastrointestinal* causes of chest pain include gastroesophageal reflux disease, esophageal spasm, peptic ulcer disease, biliary disease, and pancreatitis. *Musculoskeletal* problems such as costochondritis, intercostal muscle strain, rib fractures and chest wall tumours may cause chest pain, as may skin conditions such as herpes zoster. Chest pain may also be associated with panic attacks.

Dr. Thompson: Thank you. That is a good approach to chest pain. Alice, as an experienced resident, can you focus the approach a bit more?

Alice: In the emergency department, I am most worried about conditions that are *life threatening* and *potentially treatable*. In a patient with chest pain, I do not want to miss a diagnosis of myocardial ischemia, aortic dissection, pericarditis or serious pulmonary disease.

Dr. Thompson: What additional information would you like to have on history?

Alice: I would like to have more information about the chest pain. A chest pain history requires details about the *location, radiation, quality, severity, duration, onset, precipitating factors, aggravating factors* and *alleviating factors, associated symptoms*, and *past history* (see table 1).

I would also like to know if the patient has any risk factors for the various causes of chest pain that I am considering. In particular, I would like to know about the presence of risk factors for coronary disease, including hypertension, diabetes, hyperlipidemia, smoking, or a family history of premature coronary artery disease.

Table 1
Examples of Features of Chest Pain on History

Features	Details
Location	retrosternal, epigastric, back, unilateral, other
Radiation	to neck, jaw, arms, back
Quality	pressure, ache, squeezing, stabbing, burning
Severity	graded from 0 to 10, 0 is no pain, 10 is excruciating
Duration	seconds, minutes, hours; constant or intermittent
Onset	sudden, gradual
Precipitating factors	exertion, meals, stress
Aggravating factors	inspiration, position, exertion
Alleviating factors	rest, nitroglycerine, antacids
Associated symptoms	shortness of breath, presyncope, palpitations, diaphoresis, nausea
Past history	similar pain

Dr. Thompson: Imran, can you give us some more information about this woman's chest pain?

Imran: The pain began while she was walking her dog. The pain was retrosternal, with radiation to the jaw. She described the pain as squeezing, and graded the severity as 7 out of 10. It was associated with sweating, and a feeling of light-headedness. She has had similar but less severe episodes of chest pain with moderate exertion over the past year, but these had always been alleviated within a few minutes of rest. This time, the pain persisted even after she stopped to rest, and was still present when I saw her in the emergency department, which was approximately one hour after the onset of pain.

She had a past history of hypertension, which was treated with a diuretic. She did not know if her cholesterol level had been checked. She had a myocardial infarction 2 years prior, at which time she experienced the same quality of chest pain as the present.

Dr. Thompson: Reena, as you know, most diagnoses are made based on the patient history. With this additional information, what do you think the likely diagnoses are?

Reena: The description of the chest pain is highly suggestive of an acute coronary syndrome, either unstable angina or a myocardial infarction. Typically, such pain is described as pressure-like, squeezing or heavy in quality; retrosternal in location with radiation to the left arm or jaw, precipitated by exertion, relieved by rest or nitroglycerine, and associated with symptoms of shortness of breath, sweating, light-headedness, nausea or palpitations. Some people, especially women, have "atypical" symptoms of myocardial ischemia, where the description of chest pain does not fit the usual pattern that I have just described.

The pain due to myocardial infarction is similar to that of angina, but is usually more severe and usually lasts longer than 30 minutes. Since our patient has had severe pain lasting for about one hour, I suspect that she has had an acute myocardial infarction.

The symptoms are not typical for aortic dissection, which may present with severe "tearing" pain with radiation to the back, pericarditis, which is typically described as a sharp, pleuritic chest pain (pain worse with inspiration), relieved by sitting up and leaning forward, or pulmonary disease, which usually presents with pleuritic pain or other respiratory symptoms. However, until I hear the results of her physical examination and investigations, I will keep an open mind, and not exclude other serious causes of chest pain.

Dr. Thompson: I agree. Imran, could you tell us about the physical examination in your patient?

Imran: She appeared pale and anxious, and was in mild distress secondary to pain. Her blood pressure was 140/80 in both arms. Her heart rate was 96 and regular, her respiratory rate was 12/min and she was afebrile. The JVP was 2 cm above the sternal angle. The cardiac apex was normal. S1 and S2 were normal, and there were no extra heart sounds, murmurs or rubs. All peripheral pulses were present and equal bilaterally, and there was no peripheral edema. On chest auscultation, good breath sounds were heard bilaterally, there were no adventitious sounds, and no abnormalities on percussion. The abdomen was soft and nontender, with no bruits, organomegaly or masses.

Dr. Thompson: Reena, could you review the physical findings you would expect in a patient with myocardial ischemia?

Reena: On *general inspection*, patients often appear anxious, diaphoretic, and pale. The *vital signs* are often normal, however, there may be evidence of increased sympathetic activity (tachycardia, hypertension) in patients with anterior wall myocardial infarction, and evidence of increased parasympathetic activity (bradycardia, hypotension) in patients with inferior myocardial infarction. The remainder of the examination is often normal. However, if there is ventricular dysfunction secondary to myocardial ischemia, the JVP may be elevated, and there may be an audible S4 or S3, a pansystolic murmur at the apex due to mitral regurgitation, or bibasilar crackles on chest auscultation.

Dr. Thompson: Are there any pertinent negative findings that make other diseases less likely?

Reena: The absence of a pulse and blood pressure differential between the arms, and the absence of the murmur of aortic insufficiency make aortic dissection less likely, but do not rule out this diagnosis. The absence of a pericardial friction rub makes pericarditis less likely, although the rub may be evanescent. There are no pulmonary findings suggestive of pneumonia, such as dullness to percussion, increased tactile fremitus, bronchial breath sounds, bronchophony, and egophony. There are no findings suggestive of a pleural effusion, such as dullness to percussion, decreased tactile fremitus, or absent breath sounds. The absence of tenderness on chest wall palpation makes musculoskeletal conditions unlikely, and the absence of tenderness or masses on abdominal examination makes intra-abdominal pathology less likely.

Dr. Thompson: Imran, what laboratory investigations did you order, and why?

Imran: I ordered the following tests: a complete blood count to rule out anemia and other hematological disorders which could precipitate myocardial ischemia; electrolytes, since electrolyte disorders can precipitate arrhythmias; baseline PT and PTT, since we plan to use anticoagulant medications and we will need to monitor these parameters. The results of these investigations were normal. I also ordered cardiac enzyme levels, including creatine kinase (CK) and CK-MB, which are enzymes that are released into the bloodstream following myocardial infarction and necrosis. The levels of these enzymes were also within normal limits.

Dr. Thompson: Reena, do the normal cardiac enzymes exclude the diagnosis of myocardial infarction?

Reena: No, since levels of these enzymes do not become abnormal until about 6 hours after myocardial infarction. We should obtain serial cardiac enzyme levels to see if there is a subsequent increase in CK and CK-MB. Other markers of myocardial infarction, such as cardiac troponins, would also be helpful, but are not widely available at present.

Dr. Thompson: Were any other investigations done?

Imran: A chest Xray was done which was normal. Here is her ECG (see figure 1).

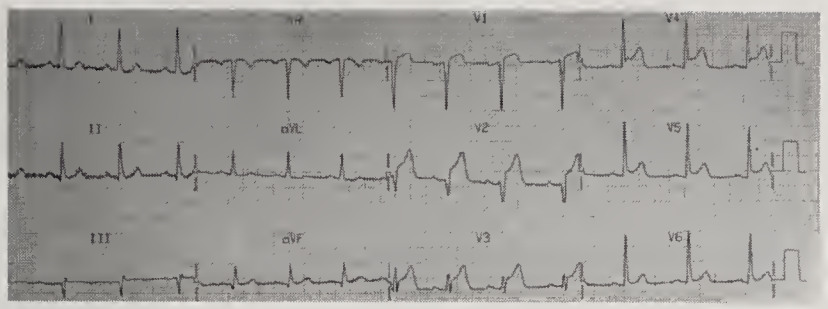


FIGURE 1. *ECG.*

Dr. Thompson: Could you interpret the ECG for us?

Imran: This ECG shows normal sinus rhythm at a rate of 75. There are Q-waves in leads II, III and AVF. There is ST elevation in leads V1 to V4. An ECG done at her family doctor's office one month ago showed normal sinus rhythm with Q-waves in leads II, III and AVF, likely secondary to a previous inferior myocardial infarction 2 years prior. However, there was no evidence of the ST elevation in leads V1 to V4 on the previous ECG.

Dr. Thompson: What are the causes of ST elevation on an ECG?

Imran: There are a number of conditions that may lead to ST elevation on ECG. These include: acute myocardial infarction, where the ST elevation occurs in the leads corresponding to the infarcted vascular territory; pericarditis, where the ST elevation is seen in multiple leads which do not correspond to a single vascular territory; ventricular aneurysm, where the ST elevation is chronic; myocardial ischemia secondary to coronary artery spasm; and benign early repolarization, where persistent ST elevation is seen in otherwise healthy young men.

In this case, the ECG changes are new, and are seen only in leads V1-V4. Together with the patient's history of chest pain, this is consistent with an acute anteroseptal myocardial infarction.

Dr. Thompson: Could you review the usual vascular supply to the myocardium, and the ECG changes you would expect to see with infarction of each vascular territory?

Imran: The right coronary artery usually supplies the inferior wall of the heart, including the right ventrical. ECG changes are seen in leads II, III and AVF. The left coronary artery usually supplies the anterior wall of the heart, including the ventricular septum, and ECG changes are usually seen in leads V1-V4. The circumflex artery usually supplies the lateral and posterior walls of the heart, and lateral ECG changes are seen in leads I, AVL, V5 and V6, while posterior changes are seen as ST depression in leads V1 and V2.

Dr. Thompson: Alice, tell us about the acute management of patients with myocardial infarction.

Alice: She needs careful monitoring of her vital signs. She should have continuous ECG monitoring and should receive supplemental oxygen if she is hypoxic. She should be given aspirin to chew as well as a beta-blocker. She is a candidate for thrombolytic therapy, which should be administered after discussing the risks and benefits with the patient. If she were not a candidate for thrombolysis, or if she were in cardiogenic shock, therapy with primary angioplasty should be considered. Ongoing pain can be treated symptomatically with intravenous morphine and nitroglycerine. She should be admitted to the coronary care unit.

Dr. Thompson: What are the contraindications to thrombolytic therapy?

Imran: Absolute contraindications to thrombolysis include suspected aortic dissection, previous hemorrhagic stroke at any time, other strokes within one year, and active internal bleeding (does not include menses). Relative contraindications include severe uncontrolled hypertension on presentation (systolic greater than 180 mm Hg and/or diastolic greater than 110 mm Hg), current use of anticoagulants or known bleeding diathesis, and trauma or prolonged (>10 minutes) cardiopulmonary resuscitation within past two weeks and surgical procedures within past 3 weeks. Other relative contraindications include noncompressible vascular punctures, recent (within 2 to 4 weeks) internal bleeding, active peptic ulcer disease, pregnancy, and a history of chronic severe hypertension that is currently controlled.

Dr. Thompson: Imran, do you have any follow-up on your patient?

Imran: She received aspirin, intravenous metoprolol, intravenous t-PA, heparin, morphine and nitroglycerine. Her chest pain resolved over the next hour. She was admitted to the coronary care unit, and has remained stable and pain-free overnight.

Acknowledgements

The authors thank Dr. Howard Leong-Poi for his careful reading of this manuscript.

Clinical Pearls

1. Experienced clinicians begin to form a differential diagnosis after hearing the chief complaint.
2. In the emergency department, the focus is on diagnosing conditions that are life-threatening and treatable.
3. Patients with common diseases, such as coronary artery disease, may present with atypical manifestations of disease.
4. A rapid diagnosis of myocardial infarction is essential since better outcomes are associated with early (ideally less than 6 hours) administration of thrombolytic agents to appropriate patients.

Further Reading

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A Feverish Frenzy

Jonathan Grynspan, BSc. (0T0) and Joanna Holland, MSc. (0T1)

Presentation of Case

A 52 year old woman from Ottawa with a 13 year history of sarcoidosis was admitted to the hospital because of fever of unknown origin of 8 weeks duration.

The patient presented 13 years earlier with dyspnea, interstitial infiltrates and mediastinal lymphadenopathy. A mediastinoscopy and lymph node biopsy were performed and a diagnosis of sarcoidosis was made. The patients was placed on oral Prednisone 10 years ago and remained on a daily dose of 10 mg/d. Several attempts to taper this dose were unsuccessful due to the onset of hypoadrenal symptoms.

Eight weeks prior to the current admission the patient experienced generalized fatigue associated with fever. This was accompanied by a right sided headache with tenderness to touch in the temples. There were no visual symptoms. A week later the patient developed shaking chills at 3:00 AM every morning, followed by fevers of 41° C, night sweats and soaking of the sheets.

Five weeks prior to the current admission the patient was admitted to another hospital for work up of her fever. Laboratory tests were performed (Tables 1 and 2). A peripheral blood smear showed microcytic anemia with atypical lymphocytes. Blood cultures performed on six separate days were all negative. Serology for EBV VCA was IgG positive. HIV, CMV, *Coxiella burnettii*, Brucellosis, and syphilis serology were all negative. Thick and thin blood films with Giemsa staining showed no malaria. Tests for antinuclear antibodies (ANA), rheumatoid factor and anti-Ro antibodies were negative. ACE level was 120 U/L (normal range 9-63). TSH was within normal limits. A tuberculin skin test as well as three anergy controls were negative. A Lumbar puncture was performed. Gram stain and india ink were negative. CSF WBC and protein were normal. Culture of CSF showed no growth. A bronchoscopy with bronchioalveolar lavage revealed no acid fast bacilli, no malignant cells and no significant growth upon culture including mycobacterial culture. Radiograph of the chest showed evidence of old parenchymal sarcoidosis. A test for fecal occult blood was negative.

Table 1
Hematological Laboratory Values
Upon Admission to Another Hospital

Variable	Value	Range
Hemoglobin (g/dl)	8.7	12.1-15.1
Mean corpuscular volume (fL)	80.5	82-100
Erythrocyte sedimentation rate (mm/hr)	48	0-20
White-cell count (10^9/(L)	5.1	3.8-9.8
Platelet count (10^9/(L)	123	125-450
Neutrophils (10^9/(L)	4.1	2.0-7.5
Lymphocytes (10^9/(L)	0.9	1.5-4.0
Partial thromboplastin time (sec)	38	22-36
INR (sec)	1.2	0.9-1.1

Table 2
Blood Chemical Values
Upon Admission to Another Hospital

Variable	Value	Range
Sodium (mmol/L)	128	136-146
Potassium (mmol/L)	3.6	3.6-4.9
Chloride (mmol/L)	94	100-109
Urea (mmol/L)	7.2	2.7-7.5
Creatinine ((mol/L)	74	<133
Glucose (mmol/L)	5.4	3.2-6.4

Abdominal and pelvic ultrasounds were normal. A computed tomographic (CT) scan of the abdomen and pelvis showed only mild hepatosplenomegaly. CT scan of the sinuses was normal. Examination of a bone marrow aspirate showed a non-specific reactive process with no evidence of lymphoma.

The patient was treated empirically with intravenous Ceftriaxone for 8 days and oral Tetracycline. Prednisone was increased to 60 mg per day. Anti Tuberculosis therapy of Isoniazid, Rifampin and Pyrazinamide was initiated. The fever did not remit. The patient was discharged after two weeks to be followed on an outpatient basis. During the following three weeks the patient continued to experience fever, fatigue as well as malaise and anorexia. The patient presented to this hospital for further investigation.

The patient had lost 26 pounds over the previous seven weeks. There was a remote history of a blood transfusion. The patient's sister had contracted pulmonary tuberculosis, however, she lived in a foreign country and the patient denied contact with her sister during her illness. The patient had moved to the Ottawa area from Belgium in 1961. She did not own any pets. The patient did not have any allergies, drink alcohol, smoke or use illicit drugs. The patient's mother was diagnosed with sarcoidosis and died of Prednisone related complications at the age of 61. There was no recent history of foreign travel. There was no eye pain, no visual changes, no chest pain, dyspnea, cough, or hemoptysis, no arthralgias or myalgias, no rashes or nodules on the skin, or GI symptoms.

The temperature was initially 38.5°C, however, during physical exam it increased to 41°C with associated decrease in mental status. The pulse was 120 and regular, the respirations were 20 and the blood pressure was 160/70. There was an orthostatic drop in blood pressure to 120/60.

The patient had moon facies and appeared flushed. There were no stigmata of infective endocarditis. There was no nuchal rigidity, and no palpable temporal artery. The pupils were equal and reactive to light and extraocular movements were normal. There was no papilloedema. There was no cervical lymphadenopathy. Apthous ulcers were visible in the orpopharynx on the buccal mucosa. Examination of the chest revealed equal air entry bilaterally, with no adventitious sounds. Cardiovascular examination revealed a normal S1 and S2 with no extra heart sounds. A grade II out of VI systolic ejection murmur was heard at the base. Abdominal examination was normal. Power was normal. There was decreased proprioception below the knee in the left leg and decreased proprioception below the ankle in the right leg. The remainder of the sensory exam was normal. Reflexes were symmetrical. Gait and coordination were normal. All pulses were intact, there were no bruits and no ankle or sacral oedema. Examination of the integumentary and musculoskeletal system were non-contributory.

Table 3
Hematological Laboratory Values During First 8 Days at This Hospital

Hospital Day	Hemoglobin (g/dl)	Mean corpuscular volume (fL)	White-cell count (10^9/(L)	Platelet count (10^9/(L)	Neutrophils (10^9/(L)	Lymphocytes (10^9/(L)
1	9.4	78.6	5.4	124	4.6	0.5
2	9.3	79.2	5.6	112	4.7	0.5
3	9.2	78.5	4.2	91	3.6	0.4
4	8.9	79.0	5.7	93	5.0	0.4
5	8.7	78.8	6.1	65	5.5	0.3
6	9.5	79.4	7.4	59	6.6	0.5
7	9.0	79.0	5.5	42	4.7	0.5
8	8.9	79.0	3.5	11	3.0	0.4

Table 4
Blood Chemical and Serological Values Upon Admission To This Hospital

Variable	Value	Range
Sodium (mmol/L)	129	136-146
Potassium (mmol/L)	3.4	3.6-4.9
Chloride (mmol/L)	95	100-109
Urea (mmol/L)	3.9	2.7-7.5
Creatinine (mol/L)	67	<133
Glucose (mmol/L)	7.6	3.2-6.4
Ionized Calcium(mmol/L)	1.08	1.13-1.28
Albumin (g/L)	31	37-48
Bilirubin (mol/L)	17	5.13-18.80
Alkaline Phosphatase (U/L)	81	36-92
Aspartate aminotransferase (U/L)	20	<38
Alanine aminotransferase (U/L)	13	<38
Gamma-glutamyl transpeptidase (U/L)	134	7-32
Creatinine Phosphokinase (U/L)	8	10-70
CK-MB	4	<5% CK

The results of hematological laboratory values during the ensuing 8 days are recorded in table 3. Biochemical findings performed upon admission are shown in table 4. A urinalysis and urine culture were negative. A peripheral blood film showed only slight microcytosis. Serial blood cultures were negative as were blood cultures for mycobacteria. Stool cultures as well as microscopic evaluation for ova and parasites were negative.

On the second hospital day oral Prednisone was tapered to 40 mg per day. Abdominal ultrasound performed on the third hospital day showed an inhomogenous liver 21cm in size, with splenomegaly, cholelithiasis and small portal nodules. A gallium scan performed on the same day showed moderate uptake of the liver and spleen. There was minimally increased uptake in both lung fields with moderately increased uptake in the left mid lung field posteriorly. A serum ferritin level performed on the 4th hospital day was 638. By the 5th hospital day the platelets had dropped to 65 (see Table 3) and continued to drop to a count of 11 on the eighth hospital day. A reticulocyte count performed on the 7th hospital day was 162 x 10^9/L (40-110). An MRI of the brain performed on the 8th hospital day was normal. A diagnostic procedure was performed.

Differential Diagnosis

Dr. Mitchell R. Weinstein: To summarize, this case involves a 52 year old woman with a background history of sarcoidosis, who has been febrile for more than 8 weeks. She has chronically been on steroids so we must anticipate some degree of immunosuppression. The patient now presents with pyrexia of unknown origin, significant weight loss, prolonged fatigue, and progressing pancytopenia.

Fever of Unknown Origin (FUO) is by definition a difficult clinical problem as there are very few clues to the etiology. My approach to FUO is based upon the different etiological possibilities. These can be separated into 4 categories. Infection has been the most frequent culprit of FUO reported in series since the 1950s, accounting for 30-40%. Neoplastic causes account for 20-30%, rheumatological conditions for 10-20%, and miscellaneous causes account for 15-20%. 5-15% of FUOs remain undiagnosed. The majority of undiagnosed cases are clinically benign. Thorough and often repeated histories, physicals and appropriate investigations including radiology, pathology and microbiology are essential in arriving at a diagnosis.

There are several possible neoplastic causes for FUO presenting with prolonged fever, weight loss, fatigue, sweats and progressive pancytopenia. Lymphoma may present with so called B symptoms and must be considered as a possible cause of this patient's current illness. Non Hodgkin's Lymphoma, intermediate or high grade or Hodgkin's disease with the corresponding 2nd peak in its bimodal incidence distribution are possible. There is a vague history of mediastinal adenopathy as well as some adenopathy seen in the porta hepatis on abdominal ultrasound. Peripheral lymph nodes may be normal with disease only in the mediastinum, abdomen or even the liver. A bone marrow aspirate and biopsy carried out on this patient, however, showed no evidence of lymphomatous involvement. This does not rule out pulmonary lymphoma, which may account for the pulmonary infiltrates observed radiographically. Furthermore, hepatic involvement can account for hepatomegaly. The absence of focal lesions speaks against hepatic involvement, however diffuse liver involvement is still possible. Further testing including a second bone marrow aspirate and biopsy should be done to rule out lymphoma, as occasionally repeated studies are needed for diagnosis. Other neoplastic disorders to consider, involving the lymph nodes and possibly presenting as FUO include malignant histiocytosis, angioimmunoblastic lymphadenopathy and Casteman's disease. This presentation is certainly compatible with the first of these but diagnosis of any of these conditions requires appropriate biopsy and pathology.

Renal cell carcinoma, the classic internist's tumor, can present with pyrexia without any localizing symptoms. The fact that this patient has a normal CT scan of the abdomen with no evidence of renal involvement and does not complain of any hematuria helps me rule out this possibility. Hepatoma,

atrial myxoma, and a variety of other malignancies may present with FUO. There is no suspicion for any of these based on our clinical history and radiology.

Several rheumatologic conditions may present with fever. Temporal arteritis is an inflammation of medium and large sized vessels that classically presents with fever, anemia, high ESR and headaches. Our patient presents with a headache of unclear duration, and there are no specific symptoms of tongue and jaw claudication, visual disturbance or tenderness along the temporal artery. I would expect her ESR and C- reactive protein to be elevated in the absence temporal of arteritis due to whatever is causing her illness therefore these values would not be very helpful. Normocytic or slightly hypochromic anemia is common but hepatic or pulmonary involvement is not. This patient's age is somewhat young relative to the typical age of presentation for temporal arteritis and she has clearly progressed despite a high dose of Prednisone.

Adult Still's disease is not uncommon in series of FUO. Onset is usually between 16 to 35 years of age. This disease classically presents with poly- or oligoarthralgias, myalgias, prolonged fevers that can be above 39-40°C for several weeks duration and an evanescent maculopapular rash on the trunk. The rash is often not appreciated and therefore presentation may be as FUO. Organomegaly and lymphadenopathy may occur in this disorder. Leukocytosis with neutrophilia, anemia of chronic disease and thrombocytosis are characteristic of this disease. Our hematological picture, the absence of joint involvement, and the patient's age as well as the lack of response to steroids argues against adults Still's disease.

There are no clinical findings other than fever suggestive of SLE, RA or Wegener's granulomatosis. The negative serology for RF and ANA argue against these as well. Pulmonary involvement occurs in 45% of patients with Wegener's at its onset. The absence of renal, sinus, skin and musculoskeletal involvement argue against this condition. We are not told of a serum ANCA level, which is sensitive and specific for active disease. Polyarteritis Nodosa (PAN) and other medium and small vessel vascultidies can present with prolonged fever. Pulmonary artery involvement does not occur in classic PAN but does in Churg-Strauss disease. Pancytopenia and the absence of renal, dermatological or neurological involvement argue against a vasculitis.

Various conditions that may present as FUO must be considered under the miscellaneous category. Sarcoidosis is a condition of unknown cause that likely results from exaggerated T helper cell response to either foreign or self antigen present in the patient's tissue. The T helper population recruits mononuclear macrophages that differentiate into epithelioid and mutinucleated giant cells and aggregate in granulomas. This patient has a thirteen year history of sarcoidosis. In this patient, the staging, degree of involvement, presenting features and indication for steroid therapy are unclear. Sarcoidosis may present with fever, although a more typical presentation is with lung involvement. Acute sarcoidosis develops abruptly over a period of several weeks, and constitutional symptoms may predominate. There are two syndromes that have been identified in acute sarcoidosis: Lofgren's syndrome, which involves erythema nodosum, joint involvement and bilateral hilar adenopathy, and the Heefordt-Waldestrom syndrome which includes fever, parotid involvement, anterior uveitis and facial nerve palsy. Pulmonary sarcoidosis is primarily an interstitial lung disease, and usually presents with dyspnea, often with cough. Most patients present with an insidious onset, usually without constitutional symptoms. This patient's serum ACE level was elevated at 120. This test is elevated in 2/3 of all patients with sarcoidosis, however, it is not very specific and can be elevated in other rheumatological and immunologic processes. The increased uptake on the gallium scan predominantly in the parenchyma of the lung is consistent with sarcoidosis although it is by no means definitive and can be seen in a variety of other infectious, neoplastic or inflammatory conditions. Sarcoidosis not uncommonly can affect the liver causing hepatomegaly and granulomas on biopsy. This is often asymptomatic but the patient's hepatomegaly could be consistent with sarcoidosis. Pathologically, 15-40% of patients with sarcoidosis have bone marrow involvement. This may result in mild anemia, neutropenia or thrombocytopenia. The extent of thrombocytopenia seen in our patient would be exceedingly rare. Furthermore, the absence of hilar adenopathy, prominent constitutional symptoms and ongoing symptoms despite high dose prednisone speaks somewhat against sarcoidosis although I can not entirely rule out this possibility.

Other miscellaneous causes of FUO include inflammatory bowel disease (IBD), thyrotoxicosis, Familial Mediterranean fever and recurrent pulmonary emboli. These can be excluded by history and clinical findings. Drug fevers must always be considered in the differential diagnosis of FUO. Drug fever can lead to pancytopenia, thrombocytopenia or anemia on an immunological basis or secondary to bone marrow suppression. At least 20% of patients have rash or eosinophilia. I haven't been told about any recent changes in medications. Additionally, when an offending drug is stopped patients usually defervesce within 3 to 4 days. I will assume that any potentially offending drug would have been stopped. There is little cause to suspect factitious fever as there is nothing on history to support this diagnosis and hematological and liver involvement would be unusual for factitious illness.

This leads us to infection, the last major category of potential cause of FUO. When approaching potential infectious

causes a very detailed history should be obtained. Areas covered should include occupational and environmental exposures, travel history, dietary history including ingestion of unpasteurized milk, contact with animals, insects or ticks and any history of sexually transmitted disease. There isn't any single algorithm which can be applied to determine all relevant laboratory tests and clinical investigations and so each case must be analyzed on an individual basis.

Tuberculosis has been the most frequent infectious cause of FUO reported in series. We are given a vague history of the patient's sister having been exposed to tuberculosis although the patient denied any exposure. The negative tuberculin skin test may not be reliable for several reasons. This patient was on corticosteroids, which are known to decrease the delayed type hypersensitivity reaction responsible for positive tuberculin reactions. Furthermore, miliary or disseminated tuberculosis has a negative skin test in up to 1/4th of all cases. Disseminated tuberculosis may present without characteristic radiographic evidence of pulmonary involvement such as miliary pattern or cavitary lung disease. There is often splenomegaly and anemia. Pancytopenia is sometimes observed due to massive bone marrow involvement and the release of various cytokines. Despite this, I would be reluctant to consider miliary tuberculosis as the cause of this patient's current illness as there are two blood cultures and a bone marrow culture that are negative for mycobacteria. Additionally tuberculosis would be unlikely in a resident of Ontario without infectious contact. However, the fact that this patient is chronically on steroids and is immunosuppressed predisposes her to reactivation disease potentially with dissemination.

A variety of series have shown intra-abdominal abscesses including retroperitoneal abscesses and intraperitoneal abscesses to be occasional causes of FUO. Certain predisposing conditions lead to intra-abdominal abscess including IBD, pancreatitis, biliary tract disease, or bacteremia. However, in our modern age with adequate imaging including nuclear imaging this is a less common cause of true FUO.

Infective endocarditis is always considered in the differential diagnosis of FUO. Aside from the fever there is not much in the present history and physical examination suggestive of endocarditis. There are no immunologic or vascular phenomena, so called stigmata of endocarditis. We are not told of any pre-existing heart disease or inciting factors (e.g. dental work, known bacteremia) that would predispose to endocarditis. The murmur that was described is more consistent with a flow murmur than the more ominous regurgitant murmur of endocarditis. This patient had multiple blood cultures taken during her stay, all of which were reported as negative. Despite empirical antibiotic therapy for approximately one week's duration I would expect blood cultures to become positive once off antibiotics for several days, if staphylococcus, streptococcus, enterococcus or gram negative endocarditis were causing fever and progressive symptoms. The so called HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella*) group of organisms are a variety of gram negative bacteria, part of the oral flora, that can produce endocarditis. They are relatively fastidious and need prolonged incubation time for growth. However, with current microbiological techniques and standard protocol that mandates keeping blood cultures for several weeks, these organisms should have been detected. There are several other etiologies of culture negative endocarditis. This includes endocarditis related to specific exposures such as *Bartonella* from contact with cats or kittens, *Brucella* from animals or unpasteurized milk, *Chlamydia psitacci* from birds, *Coxiella burnetii* from animals and ticks and *Legionella.* A number of these have been looked for serologically all of which was negative. In addition there is no specific information about predisposing exposure. Candida or other fungi which are rare causes of native valve endocarditis are often poorly cultured from the blood. The main risk factors for *Candida endocarditis* are intravenous drug use, chronic intravascular catheter, broad spectrum antibiotics and intra-abdominal surgery, none of which are described in this case.

A variety of other infective agents including EBV, CMV and HIV can cause prolonged fevers upon primary infection. These can mostly be ruled out as serology has been negative or showed evidence of previous disease as in EBV. There is no epidemiologic reason to suspect a variety of rickettsial diseases, *Ehrlichia*, or relapsing fevers. There is no evidence of UTI, osteomyelitis or septic thrombophlebitis, all of which can rarely present as FUO.

Clearly under the appropriate epidemioloigical situations a variety of parasitic infections need to be considered including malaria, schistosomiasis, leishmaniasis and filariasis. Without any travel history these can be excluded.

Aspergillosis can cause invasive pulmonary disease and occasionally extrapulmonary disease (particularly sinus or brain involvement). The main predisposition is prolonged and profound neutropenia or high dose steroid usage. Invasive disease usually shows consolidation, often with cavitation, and progresses relentlessly. This patient was never neutropenic and did not have prominent pulmonary findings.

A final category of infectious cause of FUO is endemic fungal infection. *Coccidioides, Blastomyces* and *Histoplasma* are three of the dimorphic endemic fungi that may cause systemic disease in the immunocompetent host. Each has its own unique environmental niche and exposure. *Coccidioidomycosis* in North America is seen predominantly in the South Western United States. Outbreaks have been well described

recently in the San Francisco area following the large Northridge earthquake and dust storms. It most often presents with a self limiting pulmonary syndrome although it can present with erythema nodosum, arthritis and fever. The lack of appropriate travel history makes this infection unlikely in our patient.

Blastomycosis is certainly seen in Ontario, along the St. Lawrence river valley and in the northern regions. Exposure is probably related to soil although this has not been clearly shown. Patients are typically men who work outdoors, often in parks. Blastomycosis often presents with both constitutional and respiratory symptoms as well as chronic pneumonia, and can involve the skin, bone and liver. Hematologic involvement as seen in our case would be unlikely.

I am most suspicious of a disseminated form of histoplasmosis in this patient. *Histoplasma capsulatum* is the most common endemic mycosis that we see in North America. In the United States, it is seen predominantly in the Ohio and Mississippi river valley. In Canada, it is seen in the St. Lawrence river valley. Outbreaks have been described in the Montreal area, particularly related to construction and evacuation. The natural habitat is usually soil – guano from a variety of birds or bats leads to enrichment. I suspect this patient may have been exposed to *Histoplasma capsulatum* as she resides in an endemic area. With low level exposure to *Histoplasma* only about 1% become symptomatic and over 99% remain asymptomatic. Of the people who become symptomatic upon exposure, the vast majority present with self limited pulmonary disease including pulmonary infiltrated or adenopathy. This form of histoplasmosis is notoriously difficult to diagnose on a purely clinical basis. Serology may be helpful. Presenting with hilar lymphadenopathy histoplasmosis could be confused with sarcoidosis or raise the possibility of lymphoma. About 10% of patients with symptomatic histoplasmosis go on to develop a chronic pulmonary form of disease often with cavitary formation but without adenopathy. Finally, about 10% of people with symptomatic histoplasmosis or about 1/2000 overall go on to develop disseminated disease. The majority of these patients have an underlying defect in cellular immunity such as AIDS or malignancy. It is likely that our patient had a depressed cell mediated immune response because of both sarcoidosis and glucocorticoid therapy.

Disseminated histoplasmosis can present with unexplained fever and weight loss. In its acute form it can resemble septicemia or even septic shock with respiratory distress hepatic or renal failure and coagulopathy. Patients without serious underlying immune deficits present with subacute or chronic progressive disseminated histoplasmosis manifested by fever, weight loss, malaise and other constitutional symptoms. Furthermore, specific organ involvement may lead to hepatosplenomegaly, Addison's disease, endocarditis, meningitis, cerebritis, and oropharyngeal ulcers. Oral ulcers are often helpful in diagnosis as it is usually easy to culture or stain for *Histoplasma capsulatum* from these lesions directly. Oropharyngeal ulcers are very common in chronic progressive disseminated histoplasmosis, seen in up to 60%, but are also common in subacute disease. Anemia, leukopenia, and thrombocytopenia are also common partly due to bone marrow involvement. Thus disseminated histoplasmosis could easily account for the pancytopenia, hepatosplenomegaly and oral ulceration seen in our patient.

Disseminated histoplasmosis can be diagnosed by several methods. Complement fixing antibodies are relatively sensitive, and immunodiffusion assays are quite specific (particularly anti H precipitins). Antigen detection from both serum and urine are highly sensitive and specific in progressive disseminated histoplasmosis both for diagnosis and follow up to assess response and dosage. Unfortunately antigen assays are only done by one research laboratory. Definite diagnosis is by culture. In acute progressive disseminated histoplasmosis blood and bone marrow cultures are positive in 50-90%. In chronic progressive disseminated histoplasmosis, blood cultures have lower yields, but oral lesions are nearly always positive.

In summation this is a 56 year old female with a 13 year history of sarcoidosis who now presents with ongoing fevers, oral ulcers, hepatosplenomegaly and pancytopenia. Clearly there are several diagnostic possibilities. On the top of my list is disseminated histoplasmosis although I can't exclude a lymphoma. I think sarcoidosis and tuberculosis are relatively unlikely based on the information I have been told so far. The next procedure that I would recommend at this point would include biopsy and fungal culture of the oropharyngeal ulcer as well as a repeat bone marrow aspirate and biopsy for pathology, microbiology including fungal stains and culture and flow cytometry. Blood for fungal cultures and if available histoplasma antigens could be useful as well.

Dr. Mitchell R. Weinstein's Diagnosis

1. Subacute progressive disseminated histoplasmosis
2. Lymphoma

Pathological Discussion

The diagnostic procedure was a bone marrow biopsy. Examination of the Giemsa-stained biopsy specimen (Figure 1) showed histiocytes filled with numerous basophilic spherical structures of diameter 2-3 m, consistent with *Histoplasma capsulatum*. Amastigotes of *Leishmania sp.* and *Trypanosoma cruzi* can be quite similar in size to fungal yeast forms, and are also found primarily in an intracellular location. As well, trophozoites of *Toxoplasma gondii* may also invade macrophages and appear similar, although slightly

larger. In Canada, *Histoplasma capsulatum* is the most likely of these diagnoses. To confirm this, special histologic stains for fungi may be used; these do not stain these protozoa reliably. To make a definitive diagnosis of *Histoplasma capsulatum,* however, the fungus should be cultured from clinical materials. Since colonization does not occur, as with *Candida* or *Aspergillus* species, identification of the responsible fungus ensure the correct diagnosis. Although skin testing with *Histoplasma* antigens has been useful in studying the epidemiology of infection, it is not useful for diagnosis. In endemic areas, positive skin tests simply demonstrate prior infection and do not indicate whether histoplasmosis is responsible for the current clinical signs and symptoms of the patient. As well, severely immunocompromised individuals, who are particularly susceptible to *H. capsulatum* infection, are generally anergic to skin testing.

Histoplasmosis is an inhalation-acquired mycosis. The causative agent, *Histoplasma capsulatum*, is a thermally dimorphic fungus which exists in nature as a filamentous fungus of the soil and converts to the yeast phase at body temperature. It multiplies in soil enriched by bird or bat droppings and the spores remain viable for years. Infection is acquired by inhalation of microconidia from soil contaminated with bird or bat droppings. The course of *H. capsulatum* infection varies with the size of the infecting inoculum and the age and immunologic competence of the host. Most infections (90 to 95 percent) involve small inoculums of organisms in immunologically competent persons. They affect small areas of the lung and regional lymph nodes and go completely unnoticed. Symptomatic infections fall into three categories: 1) acute pulmonary, 2) chronic pulmonary and 3) disseminated.

Inhalation of a large inoculum of spores, as occurs in an excavated bird roost or a cave where bat guano has accumulated, may cause acute pulmonary infection with extension to liver, spleen and bone marrow, even in the normal, otherwise healthy host. Inhaled spores reach small bronchioles or alveoli, and after 2 or 3 days germinate and release yeast forms of the fungus, which are phagocytosed by macrophages. The yeasts proliferate within the phagocytes, and more macrophages are recruited, many of which also become infected. From the lung foci, infected macrophages migrate to the mediastinal lymph nodes, spleen and liver. Epithelioid cell granulomas are produced, and usually undergo coagulative necrosis and coalesce to produce large areas of consolidation, but may also liquefy to form cavities. As healing progresses, spontaneously or following drug control in normal hosts, the end result is a dense, contracted lesion with prominent fibrosis, and calcification, often encapsulating areas of caseous necrosis. Yeast forms often persist within these healed lesions for many years without consequence, but in rare individuals, the persisting yeast forms stimulate progressive fibrosis, potentially resulting in damage to structures of the mediastinum. Over many years, the pulmonary veins, superior vena cava, pulmonary arteries and esophagus may become compressed. In most cases, however, acute pulmonary infections resolve without the need for antifungal therapy, and patients become asymptomatic within 2 to 6 weeks. Patients with this form of histoplasmosis may present with nonproductive cough, fever, chills, malaise, myalgia and dyspnea.

In patients with structural abnormalities of the lung such as emphysema, chronic pulmonary histoplasmosis may occur. This may immediately follow the acute pulmonary form, or become clinically apparent after a long dormancy. Usually found in middle-aged or older cigarette smoking men, this condition involves cavitary lesions evident on chest radiographs and symptoms of fever, weight loss, malaise and copious sputum production. The yeast takes advantage of structural defects of the lung to colonize abnormal pulmonary spaces. It is thought that emphysematous damage to the pulmonary apices may impede access of immune cells to the infected area, resulting in a chronic obstructive disease in the apical areas of the lung, often mistaken for tuberculosis. Granulomas are usually present at the apices of the lung, with retraction and thickening of the pleura, and in the hilar nodes. Further progression involves more and more of the lung parenchyma, with cavity formation in about 20 percent of cases. If untreated, approximately one third of cases stabilize or improve spontaneously early in the course. The remainder progress insidiously, compromising pulmonary function. Death may result from cor pulmonale, respiratory failure or bacterial pneumonia.

The most severe and life-threatening form, disseminated histoplasmosis, usually occurs in infants, the elderly and in patients with cellular immune deficiency, although it occasionally occurs in persons with no known immune defect. The most common clinical setting for this often fatal condition is AIDS. It is also seen in patients with lymphoreticular neoplasms, patients undergoing immunosuppressive chemotherapy such as for organ transplantation, patients with sarcoidosis, or patients receiving steroids. Disseminated histoplasmosis is characterized by progressive organ infiltration with macrophages containing *H. capsulatum.* The extent of persisting macrophage infection varies from enormous numbers of heavily parasitized cells to a few, lightly parasitized cells. The course and pathology of the infection depends on the degree of host immunodeficiency. In mild cases, the host response is sufficient to inhibit, but not eliminate the infection. For long periods of time, the disease remains largely confined to the macrophages in the lymph nodes, bone marrow, liver and spleen, although there is often orpoharyngeal involvement as well. Aggregates of macrophages contain a few *H. capsulatum* yeast. In the mildest cases, granulomas sometimes form. In cases of profound immunodeficiency, there is little restraint on the pro-

liferation of the fungus. Granuloma formation does not occur, rather there are foeal aeeumulations of mononuelear phagocytes filled with fungal yeasts throughout the tissues and organs of the body. Eventually large elusters of maerophages filled with *H. capsulatum* may infiltrate the liver, spleen, lungs, intestine, adrenals and meninges. The aeeumulation of infected maerophages displaees and destroys the affeeted tissues. Infeetion of the retieuloendothelial system accounts for most signs, and thrombocytopenia, anemia and leukopenia frequently oecur. While pulmonary manifestations are usually expeeted with histoplasmosis, in the disseminated form of the disease lung involvement is not always seen, exeept in the most severe eases. Other eommon findings inelude, fever, night sweats, weight loss, hepatosplenomegaly, generalized lymphadenopathy and GI uleeration, espeeially in the oropharyngeal area. Patients may also have symptoms of Addison's disease from massive involvement of the adrenal glands. Untreated, this form of infeetion may be rapidly fatal.

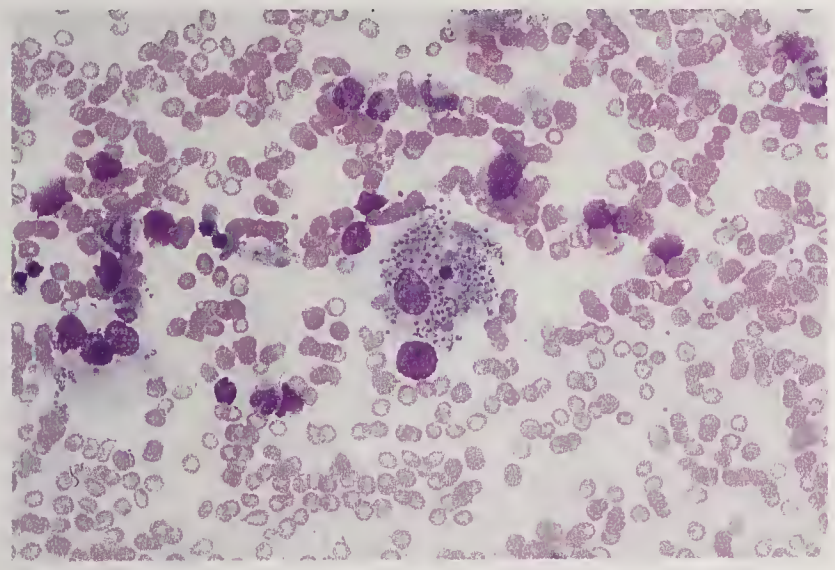


FIGURE 1. *Bone marrow biopsy specimen showing histiocytes filled with numerous compact fungal Histoplasma capsulatum cells. (Giemsa)*

Pathological Diagnosis

Disseminated Histoplasmosis

Conclusion: Dr. Mitchell R. Weinstein

With the established diagnosis of disseminated histoplasmosis antifungal therapy should be initiated. The drug of ehoiee has elassieally been Amphoteriein B, and elinical improvement occurs in most patients with disseminated disease within 1 week. Reeent data has also shown good response in patients with AIDS, with mild to moderate severity of disease treated with Itraeonazole. I would reeommend intravenous Amphoteriein in this patient, with a step down to Itraeonazole onee she has responded. Therapy is usually eontinued for at least 6 months.

One remaining question raised by this ease is the relationship between disseminated histoplasmosis and sareoidosis. Several similar eases have been deseribed. It has been suggested that sareoidosis may predispose to disseminated histoplasmosis by deereasing cell mediated immunity. As well, eortieosteroid therapy for sareoidosis, as used in this patient, may contribute to the association. As I mentioned in the diseussion the initial presentation of pulmonary histoplasmosis with lymphadenopathy may be misdiagnosed as sarcoid; pathology of both reveals granulomas and without speeific mierobial and serologieal studies histoplasmosis ean easily be missed. Most cases of disseminated histoplasmosis oeeur after primary infection or re-infeetion, but it ean also oeeur after endogenous reaetivation, partieularly with advancing age and immunosupression (ineluding steroid use). It thus remains unelear if the patient in faet had sareoidosis to begin with.

Acknowledgements

The authors wish to thank Drs. B. Mullen and B. Patterson for their eontribution to this ease.

Paediatric Grand Rounds

Thomas Roger Harris, BSc., and Laura Catherine McAdam, MSc.

Case Histories

Case 1

Brian W. McCrindle, MD, FRCPC
Division of Cardiology, Hospital for Sick Children

An asymptomatic 2 year old boy presented to a dermatologist for removal of skin lesions (Figure 1). Screening laboratory investigations were normal except for a total cholesterol of 26.47 mmol/L. LDL levels were 24.73 mmol/L, and triglyceride levels were normal.

FIGURE 1. *Photograph of (a) the dorsal aspect of the hand, and (b) back of the ankle, showing skin lesions.*

What is the most likely diagnosis?

Case 2

Brian W. McCrindle, MD, FRCPC
Division of Cardiology, Hospital for Sick Children

A 9 month old boy initially presented with desquamation of the hands and feet. Three weeks ago he had an illness with 15 days of persistent fever, bilateral conjunctivitis, cheilitis, cervical adenopathy, generalized rash, and palmar and plantar erythema with swelling. Coronary angiograms at 3 months after the illness are shown in Figure 1.

FIGURE 1. *Selective coronary angiography of the (a) right and (b) left coronary artery systems.*

What is the most likely diagnosis?

Case 3

M.A. Marcon, MD, FRCPC
Division of Gastroenterology and Nutrition, Hospital for Sick Children

A 12 year old female presents with abdominal pain that has been on and off for 6 months. She has 3 to 4 loose stools per day. Her hemoglobin is 96 g/L. As part of her diagnostic investigation she has a colonoscopy with biopsies (Figures 1 and 2).

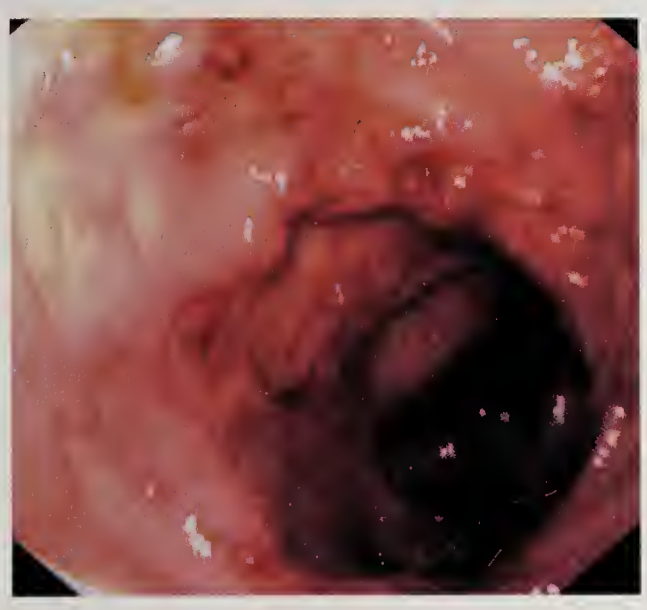
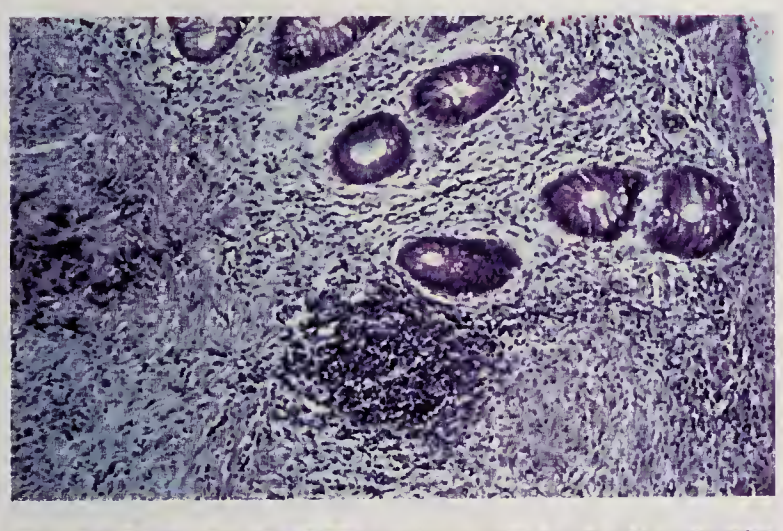


FIGURE 1. *Photograph from her colonoscopy.*



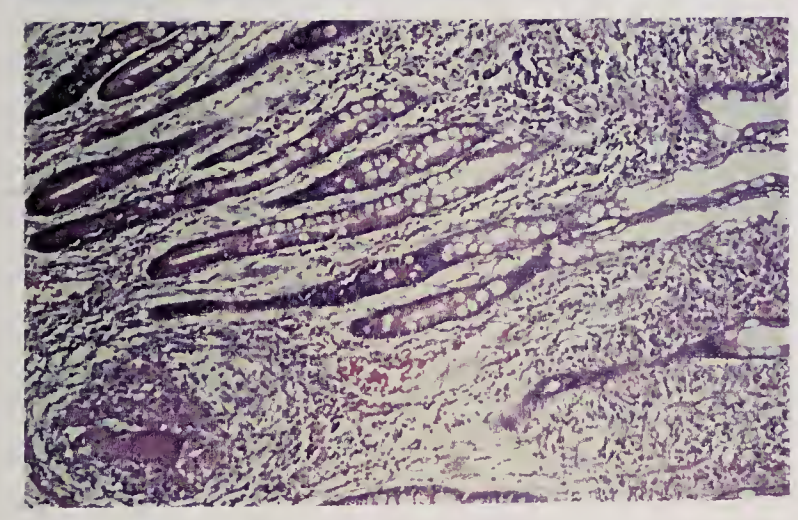


FIGURE 2. *Histology of the (a) colonic and (b) ileal biopsies.*

What is the most likely diagnosis?

Case 4

M.A. Marcon, MD, FRCPC
Division of Gastroenterology and Nutrition, Hospital for Sick Children

A 10 year old boy presents with the complaint of mild intermittent abdominal pain, but no diarrhea, fever, vomiting, or weight loss. He is shorter than his older brothers were at 10. His younger brother has Type 1 diabetes. He has a hemoglobin of 100 g/L. Figure 1 and 2 are his small bowel biopsies.

FIGURE 1. *Small Intestinal biopsy viewed via a dissecting microscope.*

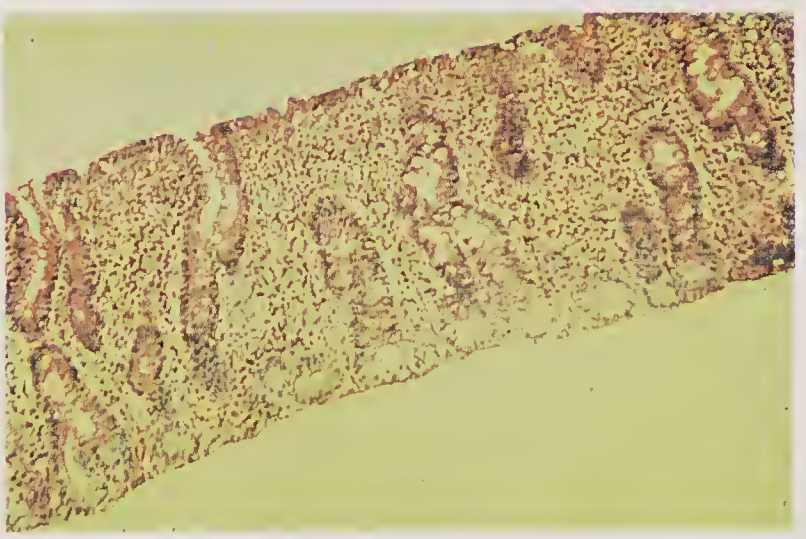


FIGURE 2. *Duodenal biopsy.*

What is the most likely diagnosis?

Case 5

Jeff Kobayashi, MD, FRCPC
Division of Neurology, Hospital for Sick Children

A 13 year old girl with a facial rash (Figure 1) is seen in the office. The history reveals that she has epilepsy and is in a special education class. Fundoscopic examination is performed (Figure 2) and a CT scan is ordered (Figure 3).

FIGURE 1. *Photograph of skin lesions.*

FIGURE 2. *Photograph of fundus oculi.*

FIGURE 3. *CT scan.*

What is the most likely diagnosis?
What else would you expect to find on physical examination?

Case 6

Alan Daneman, MB, BCh., BSc., FRACR, FRCP(C)
Department of Radiology, Hospital for Sick Children

A 6 month old boy presents with a 12 hour history of vomiting, colicky abdominal pain, current jelly stool, and a palpable abdominal mass in the right upper quadrant. Findings on abdominal sonography and plain radiograph are shown in Figures 1 and 2 respectively.

FIGURE 1. *Abdominal sonogram of right upper quadrant shows the mass (shown by electronic x and + cursors).*

FIGURE 2. *Abdominal radiograph shows right abdominal mass (arrow).*

What is the most likely diagnosis?
What is the next procedure to perform?

Case 7

Denis Daneman, MB, BCh., FRCPC
Chief, Division of Endoerinology, Hospital for Siek Children

A 10 day old infant presents with a 3 day history of vomiting, weight loss, and dehydration. Pregnancy, labour and delivery were uneventful. At birth the child was thought to be a male with severe hypospadias and bilateral cryptorchidism (testes not palpable) (Figure 1). On admission, serum sodium was 118 mmol/l and potassium was 9.6 mmol/l.

FIGURE 1. *Photograph of genitalia.*

What is the most likely diagnosis?

Diagnosis

Case 1

Tuberous Xanthoma Secondary to Homozygous Familial Hypercholesterolemia

Physieal manifestations of hyperlipidemia are extremely rare in ehildren. The extreme elevations of LDL eholesterol with normal triglyeerides suggest the diagnosis. The skin lesions are tuberous xanthomata, whieh oeeur over extensor surfaees, as well as the buttoeks, skin ereases and within extensor tendons. Familial hypereholesterolemia is an autosomal dominant eondition assoeiated with absent or defeetive LDL reeeptors, and premature atheroselerotie eardiovaseular disease in the 4th and 5th deeades. Patients who are homozygous for this condition (ineidenee 1:1,000,000) tend to be unresponsive to lipid lowering medieation, and require regular plasmapheresis to reduee LDL levels.

Case 2

Coronary Artery Aneurysms Secondary to Kawasaki Disease

Kawasaki disease is an aeute systemie vaseulitis of unknown etiology with a peak ineidenee between 1 to 4 years of age. It has beeome the most eommon cause of aequired heart disease in ehildren in developed countries. Appropriate therapy with intravenous gamma globulin within 10 days of fever onset reduees the risk of eoronary artery aneurysms from about 25% to 4%.

Case 3

Ileal-Colonic Crohn's Disease

On eolonoseopy there were areas of abnormality eharaeterized by seattered uleeration, thiekened mueosa and some pseudopolyp formation. These were surrounded by normal appearing mueosa (Figure 1). Biopsies from this area, as well as the terminal ileum, showed inflammatory infiltration and some biopsies eontained non-easeating granulomas.

Case 4

Celiac Disease

This young man turned out to have eeliae disease. The biopsy shows the elassie histologie findings: loss of villus strueture, hypertrophy of the erypts and intraepithelial lymphocytes and eosinophils. With the disseeting mieroseope one ean see the finger like projeetions in the normal bowel and the obvious laek of these in the celiae patient.

Case 5

Tuberous Sclerosis

Tuberous selerosis is a neuroeutaneous disorder. A hallmark of the disorder is the adenoma sebaeeum (an angiofibroma), whieh is distributed in a butterfly pattern over the eheeks, ehin, and forehead. Rhabdomyoma of the heart (imaged by ultrasound), hamartoma of the retina and tumorous malformations (angioleiomyomas) of the kidney, liver, adrenal glands, and panereas are also eharaeteristie of this disorder. The disorder is inherited as an autosomal dominant trait (ehromosome 9 or 16). In the brain multiple ealeified nodular tumors, eomposed of abnormal neurons and glial cells, often lie in the plane of the eerebral eortex.

Case 6

Ileocolic Intussusception

The ultrasound shows the classic features of the target sign of an intussuseeption. The arrow indieates the eehogenie (white) mesentery between the two layers of the intussusceptum. The plain radiograph shows a nonspeeifie mass. These intussuseeptions most eommonly oeeur in ehildren between 3 months and 2 years of age and are usually due to hyperplasia of the lymphoid tissue in the distal ileum. The next procedure to be eontemplated is a therapeutie air or eontrast enema under fluoroseopie or sonographie guidanee to attempt reduetion if there is no elinieal evidenee of peritonitis. Sueh nonoperative reduetion aehieves 80-90% sueeess rates.

Case 7

21-Hydroxylase Deficiency

Female infant with 21-hydroxylase deficient salt-losing eongenital adrenal hyperplasia. This eondition is assoeiated with both glueoeortieoid and mineralocortieoid deficieney eausing the salt-losing erisis, and androgen exeess eausing virilization of the female external genitalia. Diagnosis depends on demonstration of an elevated 17-hydroxyprogesterone eoneentration (i.e. steroid metabolite proximal to enzyme bloek).

Medical Computing Today Website

Jeff Kwong, BSc. (0T1)

Medical Computing Today (http://www.medicalcomputingtoday.com) is a "not-for-profit Website publishing peer-reviewed articles on computers and related technology for physicians and other health professionals." For those who complain about the volume of "junk" one comes across on the World Wide Web, this is actually a very good site that all health professionals and students should bookmark.

The site contains a number of articles written and peer-reviewed by practicing physicians. The core members of authors come from among long-time reviewers or Advisory Board members of Healthcare Computing Publication's *Medical Software Reviews*, but contributions from others are welcome as well. The articles on this site range from original scholarly works to opinion pieces of current trends in medical computing, from reviews of web sites and resources to reviews of the latest American Boards examination preparation software packages for various specialties.

The growing field of medical computing encompasses a wide array of topics, including telemedicine, computers in medical education, electronic patient records, computer-based evidence-based medicine, and web resources for patient education, to name just a few. (If you want to know more about each of these, I suggest checking out the site). MCT succeeds in covering most of today's hot topics, or at least in providing links to other sites or references.

For the more traditional, *Medical Computing Today* also includes a small collection of resources for selected medical topics. For instance, an article on Multiple Sclerosis provides an introduction to the disease and reviews a plethora of links for medical education, MS organizations, updates of the latest research, journals, on-line resources, sites for patient education, and other MS web sites. I was quite impressed by the comprehensiveness of the links - somebody spent a lot of time digging up all these sites! Futhermore, all the information and linked web sites have been critically reviewed so that one can quickly determine a link's relevance and usefulness. The only problem is that only a few topics have been so thoroughly researched. I am hoping that many more topics will be added in the near future. If so, this site would be nearly unparalleled as a first place to look on the web when searching for information on a particular condition.

The site is quite user friendly, allowing for the surfer to browse the articles categorically (Clinical Computing, Medical Education, Medical Informatics, the Internet, and Specialties) or chronologically (Archives). There is a What's New section so that return viewers can skip right to the latest updates. A search function allows the viewer to search for words or phrases in all the articles and features, and there is also a site map for those who are more visually-inclined to navigate the site more easily. Finally, the layout is concise but kept simple, thereby avoiding tedious download times.

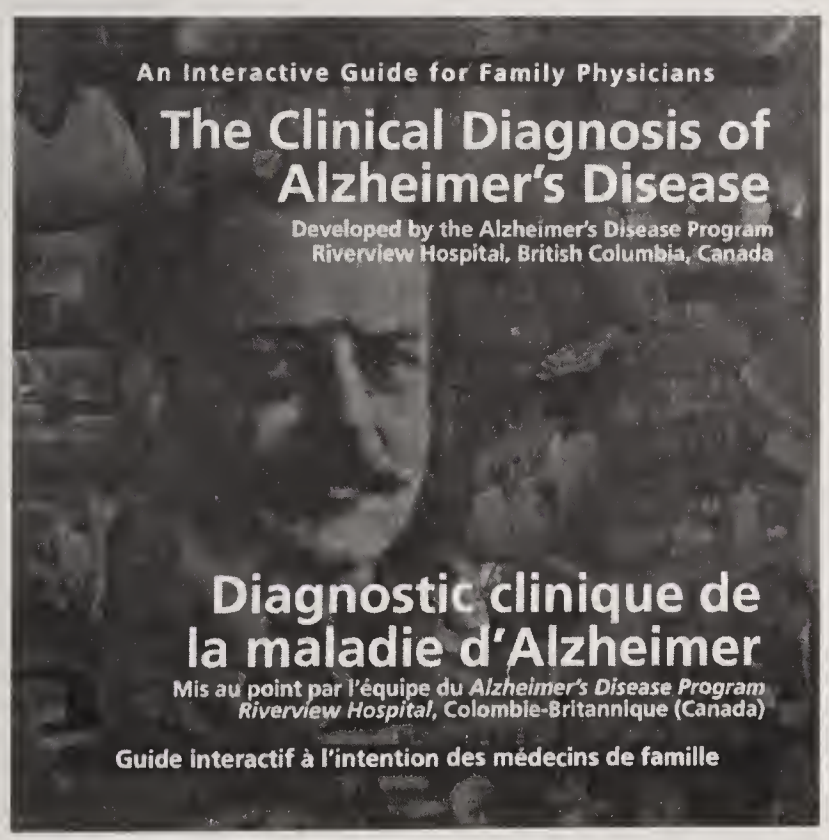
Medical Computing Today is useful both as an introduction to the uninitiated and also as a source of expert information for those already involved in this quickly evolving area of medicine. It targets a wide audience and achieves both breadth and depth, at least in topics of medical computing. I will conclude by predicting that no future health professional will be able to avoid the pervasive influence of computers and computing technology in the field of medicine. Since we'll all have to deal with this sooner or later, it may as well be sooner rather than later . . . so go check out http://www.medicalcomputingtoday.com today!

Clinical Diagnosis of Alzheimer's on CD-ROM

Heather McArthur, BSc. (OT1)

The Clinical Diagnosis of Alzheimer's Disease: An Interactive Guide for Family Physicians CD-ROM was developed by Dr. H. Karlinsky and members of the Alzheimer's Disease Program at Riverview Hospital in British Columbia. It is designed to provide family physicians and other health care professionals with comprehensive information pertaining to the clinical diagnosis of Alzheimer's Disease (AD).

The program is organized into eight sections. These provide general information about AD, guidelines for eliciting an appropriate patient history, guidelines for performing effective physical and Mini-Mental State examinations, the criteria by which AD is diagnosed, as well as the theory and appropriateness of laboratory investigations and neuroimaging in diagnosing AD. The General Introduction provides historical details of AD diagnosis in addition to a general overview of relevant aspects of the disease. The Patient History section then describes the cognitive, non-cognitive and functional ability changes frequently observed in AD patients, while outlining specific clinical approaches to relevant personal and medical history. The Physical History section reviews details of physical and neurological examination. The Cognitive Assessment section describes effective administration of the Mini-Mental State examination as well as outlining the relevance of pertinent findings. The Laboratory Investigations section reviews recommended laboratory tests and their relevance, while the Diagnostic Neuroimaging section provides introduction to the diagnostic imaging tools. The Clinical Diagnosis section outlines diagnostic criteria and presents guidelines for differential diagnoses. The Case Study section provides an excellent summary of the aforementioned principles by providing an interactive case study which permits the user to evaluate diagnostic abilities. The comprehensive nature of each section, the facility with which one may navigate between each of the sections, the clear and succinct presentation of key practice tips, the self-evaluation with instructional feedback and the extensive use of multimedia images combine to generate an extremely powerful and effective tool in understanding and diagnosing Alzheimer's Disease.


An Interactive Guide for Family Physicians
The Clinical Diagnosis of Alzheimer's Disease
Developed by the Alzheimer's Disease Program
Riverview Hospital, British Columbia, Canada
Diagnostic clinique de la maladie d'Alzheimer
Mis au point par l'équipe du Alzheimer's Disease Program
Riverview Hospital, Colombie-Britannique (Canada)
Guide interactif à l'intention des médecins de famille

There are many features of this software which render it accessible, effective, versatile and enjoyable to use. Firstly, the CD is highly accessible as it is provided gratis by the Alzheimer's Society of BC and can be operated in either French or English. Secondly, both PC and Mac requirements are supported on the same CD. The presentation is clear and succinct, using unassuming language such that the user is neither overwhelmed nor intimidated. Furthermore, the use of videos, photographs, animations, graphics and motion videos effectively illustrate critical concepts. For example, one can see first-hand through video presentation how a patient with AD might present and what signs and symptoms might emerge as the individual's disease progresses. This presentation also allows one to differentiate between appropriate and inappropriate means for conducting an interview. The effective use of multi-media techniques is further augmented by the authors' attention to detail. For example, the patient's experience during the various neuroimaging techniques are presented with animation. Not only do the animations illustrate the patient's physical experiences while undergoing these investigations, but they also incorporate sound bytes such that the user can share the patient's auditory experiences. A further attribute of the program is the frequent use of self-evaluation techniques. Each segment is followed by a series of questions, often accompanied by appropriate multimedia illustrations, which allow the user to self-evaluate his or her understanding of the material presented. The self-evaluation is interactive and provides effective instructional feedback.

The clear and succinct nature of the presentation, the effective use of multi-media to illustrate key concepts, the accessibility of the language and concepts, the facility with which one can navigate between each segment and the opportunity for self-evaluation make this CD-ROM a highly effective tool for family physicians to improve their ability to diagnose Alzheimer's Disease. These same features make the CD appropriate for other health care professionals and medical students interested in augmenting their understanding of this prevalent disease. Furthermore, the CD is so user-friendly and enjoyable to use that it may provide a great resource for family members of patients with Alzheimer's Disease to better understand the experiences, medical investigations and cognitive, non-cognitive and functional changes relevant to their loved one's experience with this insidious disease.

C : \ Quick \ Reference \ Review

Novartis

List Price: $0 (provided gratis from the Alzheimer's Society of BC)

Rating (out of 5): ****

System Requirements:

Compatible with Windows 95, Windows 3.1 and Macintosh

NaturBase® Lite and Professional CD-Rom

Dan Perri, BSc.Phm. (OTO)

NaturBase® is a software package that can be used both by the public and by health providers interested in learning more about herbal therapies. It comes in two versions: a Lite Version, which contains 314 herbal abstracts (1912 Synonyms), and a Professional Version, which contains 830, abstracts (3875 synonyms). The latter version also contains more illustrations and dictionary search terms, a greater number of searchable indications and actions, and a hugely expanded nutrient and chemical constituent database. While both offer Internet and e-mail connectivity, the Pro Version offers an Internet update utility by subscription. The CD is dual-version, so users not satisfied with the scope of the Lite Version can upgrade to the Pro Version at any time.

Navigation through the program is quite straightforward. Pop-up help prompts appear for almost every function and placing the cursor over hypertext words causes a definition or explanation to appear. *NaturBase*® consists of six tabbed pages with the color-coded tabs located at the top of the screen. For the most part, the screens are laid-out in the same manner. The upper-left corner is reserved for diagrams or pictures, the lower-left corner is a list of search results, the upper-right (most of the screen) is the information or product monograph area (referred to as the "hypertext window" throughout the program) and below this is a window in which the user may add his or her personal notes which are saved and re-opened whenever returning to that particular herb entry. At the very bottom of the screen is a toolbar, which contains a variety of buttons that control various functions including: copy, print, options, Internet updates, email, help, and bibliography. Colors, fonts, and window-sizes may be altered to the user's preference through the options button. Herbal monographs may be sent as e-mail messages and users with the upgraded features can download files by clicking on the Internet update button. While the bibliography is extensive, it is not arranged under herb or indication and there is no notation throughout the text making it difficult to do a personal literature search.

The search features of *NaturBase*® are quite good, enabling the user to conduct searches by herb (common and Latin binomial names), indication, homeopathic indication, geographic region, herbal actions, and chemical constituents and nutrients. The information contained is quite accurate with regards to contraindications, side effects, drug interactions, and precautions of herbal products. The indication and action sections represent a list of diseases or herbal properties that have more of a historical or anecdotal basis than a pharmacologic one. (Even though most of the works listed in the bibliography are credible, many are of historical significance or present the actions/indications of various herbs as "traditional uses" or "traditional properties.") While it may be true that little is known of the mechanisms of action for many herbs, recent studies do provide laboratory evidence of phytopharmacologic effects. *NaturBase*® does not report any of this, perhaps in part due to the fact that the program is aimed more at the herbal self-medicator, health-food store clerk, or complimentary healer than the allopathic physician. (It should be noted however that the pharmacology of the nutrients and known components of herbs are described when searching by constituent.)

In summary, *NaturBase*® is a complex database of information on herbal medicines and nutritional supplements. While it lacks evidence-based therapeutics or pharmacologic information, it is accurate and thorough in its presentation of the adverse effects, contraindications, and drug-herb/nutrient-herb interactions. It is this latter information which should most interest the physician, pharmacist, or primary care nurse in assessing the safety of a patient's self-medication with "natural" products within the context of concurrent medications and disease states. In essence, for the health provider who is not prepared to recommend herbal therapy but who does not have a closed mind, it is a powerful tool in assessing the relative safety of phytopharmaceuticals.

C : \ Quick \ Reference \ Review

3DTX Corporation (www.3.dtx.com)

List Price:Lite Version $39.95 (US), Pro Version $89.95 (US)

Rating (out of 5): *** 1/2

System Requirements:

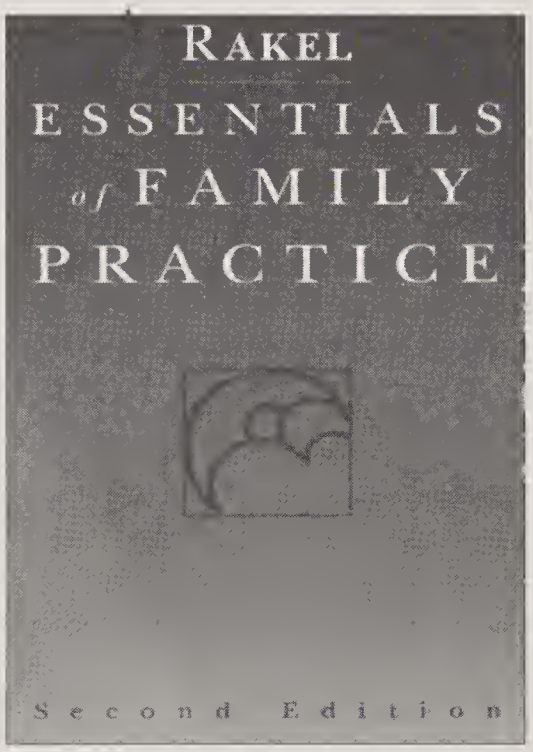
Windows 3.1, 95 or NT

Essentials of Family Practice, Second Edition

Reviewed by Orit Freedman BSc. (0T2)

Editor: Robert E. Rakel
Publisher: W.B. Saunders Co.
Date of Publication: 1998
Number of Pages: 626

Overall:	8/10
Strengths:	Easy to comprehend; interesting to read; self-contained chapters.
Weaknesses:	Geared to a U.S. audience; provides little general medical background.
Audience:	Medical students and family practice residents.



Essentials of Family Practice is a textbook designed to serve as a supplement to the *Textbook of Family Practice* (also edited by R. Rakel), a standard text in the field of family medicine. It has been significantly revamped from its first edition, with all chapters being either new or revised and updated. The book consists of two parts: twelve chapters discussing topics fundamental to the field of family practice, followed by seventy-one clinical cases presented as they would be to a family physician. The selected cases represent the most common diagnoses made by family doctors, and for each case, a differential diagnosis is developed using problem-solving methods.

Essentials of Family Practice is an interesting and well-written text that even a med-neophyte, such as myself, could comprehend. The first four chapters discuss general topics of interest in family medicine, including the definition of a family physician, ethics in family medicine, family dynamics, and patient compliance. These chapters, combined with the next four which become focused upon general problem solving in family practice, provide a broad yet comprehensive overview of what family practice entails. These chapters are interesting, easy to read, and useful to anyone considering a career in family medicine. Included in the first section of the text is a chapter on interpreting lab tests which summarizes the most common laboratory tests performed, when they are employed, and what the results mean. Each chapter, and indeed the case studies that follow, are self-contained in that none rely upon a previous chapter, hence it is easy to read only those topics of interest and relevance at any given time.

The second section of the text, devoted wholly to case studies, is fascinating yet impossible to comprehend without a general medical background. Given that *Essentials of Family Practice* is but a companion to the *Textbook of Family Practice*, a 2000-page text entirely devoted to providing this general medical background, it isn't really fair to expect more. The case studies include topics that have not always been formally recognized as being medical issues, including domestic violence and the role of the family doctor in managing pain in the terminally ill. Moreover, one chapter is devoted to approaches to patients who smoke, a topic which almost certainly would not have been included in a mainstream textbook as recent as five years ago. The case studies are recommended for those who want practice in applying their knowledge of general medicine and for those writing qualifying exams, as each chapter reviews a full case history, differential diagnosis, tests to perform, results, and follow-up treatment. In addition, references and practice test questions follow each case history.

One major drawback of the text is that *Essentials of Family Practice* is written for an American audience, and so some of the chapters and topics (especially those dealing with the state of the health care system and the role of the family physician in that system) are less relevant to those practicing in Canada. Furthermore, statistics and studies cited are for the most part relevant to the United States. Unfortunately, as of yet there is simply no equivalent Canadian text.

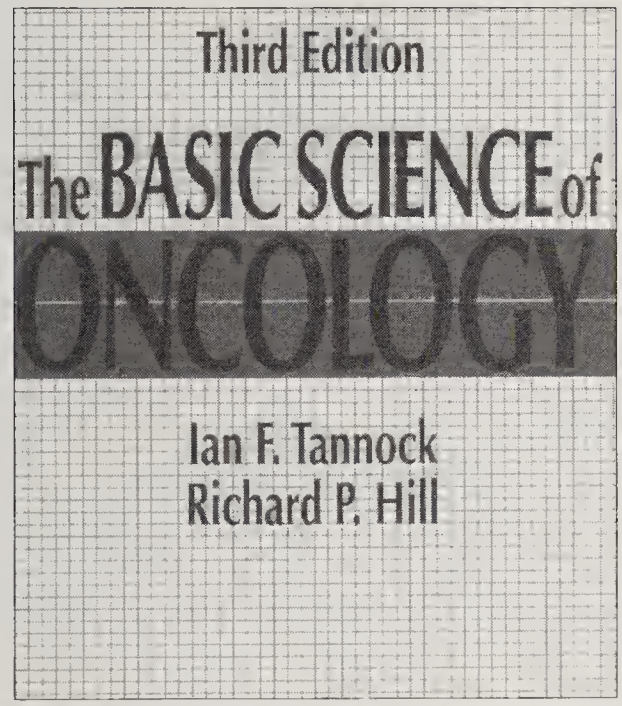
In summary, I would recommend buying *Essentials of Family Practice* only for those certain of a career in family medicine. However, for those who have yet to choose a career path, this is an ideal text to flip through in order to gain understanding on what it means to be a family physician.

The Basic Science of Oncology, Third Edition

Reviewed by Samir C. Grover BSc. (0T1)

Editors: I. F. Tannock and R. P. Hill
Publisher: McGraw-Hill Inc.
Date of Publication: 1998
Number of Pages: 539

Overall:	7/10
Strengths:	Well referenced index
Weaknesses:	Significant proportion of figures are of poor quality
Audience:	Undergraduate students in science, medical students



With the significant technical advances in cell biology and the advent of automated molecular biology techniques and other related technologies in the late 1980's and early 1990's, there have been significant advances in the molecular aspects of cancer biology in the past decade. In this regard, the compilation of a sequel to the acclaimed last edition of *The Basic Science of Oncology*, published in 1992, was somewhat overdue, as its editors readily acknowledge. In this third incarnation, Drs. Tannock and Hill have substantially revised and restructured their text to incorporate these advances, and as a result have generated an easy-to-read, comprehensive and updated compendium of the basic scientific principles of oncology and cancer therapy.

The book is divided into twenty chapters, the majority of which have been written by researchers associated with the University of Toronto. The first three chapters are basic in their scope and introduce the field of cancer biology, the epidemiology of cancer, and the cytogenetic techniques currently used in cancer research. The following two chapters are dedicated to the genetic basis for cancer while underscoring fundamental concepts, such as oncogenes and tumour suppressor genes. The sixth chapter, dealing with growth factors, signal transduction and signalling pathways is a new addition to this edition, and incorporates elements of recent research into intracellular signalling. The subsequent five chapters deal with topics including the cell cycle and apoptosis, chemical and radiation carcinogenesis, tumour growth and metastasis, and the role of hormones in carcinogenesis, with considerable emphasis placed on basic immunology and endocrinology. Elements of radiation, chemical, biological, and other forms of therapy are discussed at length in the penultimate seven chapters, with the final chapter serving as a synopsis of the interpretation of studies of diagnostic tests and clinical trials discussed previously.

Despite its many contributors, the text bears a homogeneous appearance, with each chapter maintaining a similar style of presentation. Each chapter provides a concise interpretation of a broad field without appearing overly laconic, yet still provides an adequate introduction to the topic discussed. Indeed, it is this simple explanation of basic scientific concepts related to a particular facet of oncology that increases the appeal of this text to undergraduate students with little background in oncology. This appeal is furthered by the well referenced index and glossary of over 350 terms. In the event that more detailed information is required, each chapter is thoroughly referenced – using the pleasing style of parenthetical citation – with a significant proportion of relatively recent references. The figures, however, are somewhat of a disappointment, especially in the first ten chapters: the majority of them are simple line drawings and schematics (which often could have been substituted or complimented with more demonstrative colour photographs), and often appear overly spartan. As with any text containing articles written by different authors, these elements still differ from chapter to chapter, with some contributions – especially the chapter regarding cellular and molecular basis for chemotherapy – standing out by virtue of their pleasant writing style, copious references and well-organized figures.

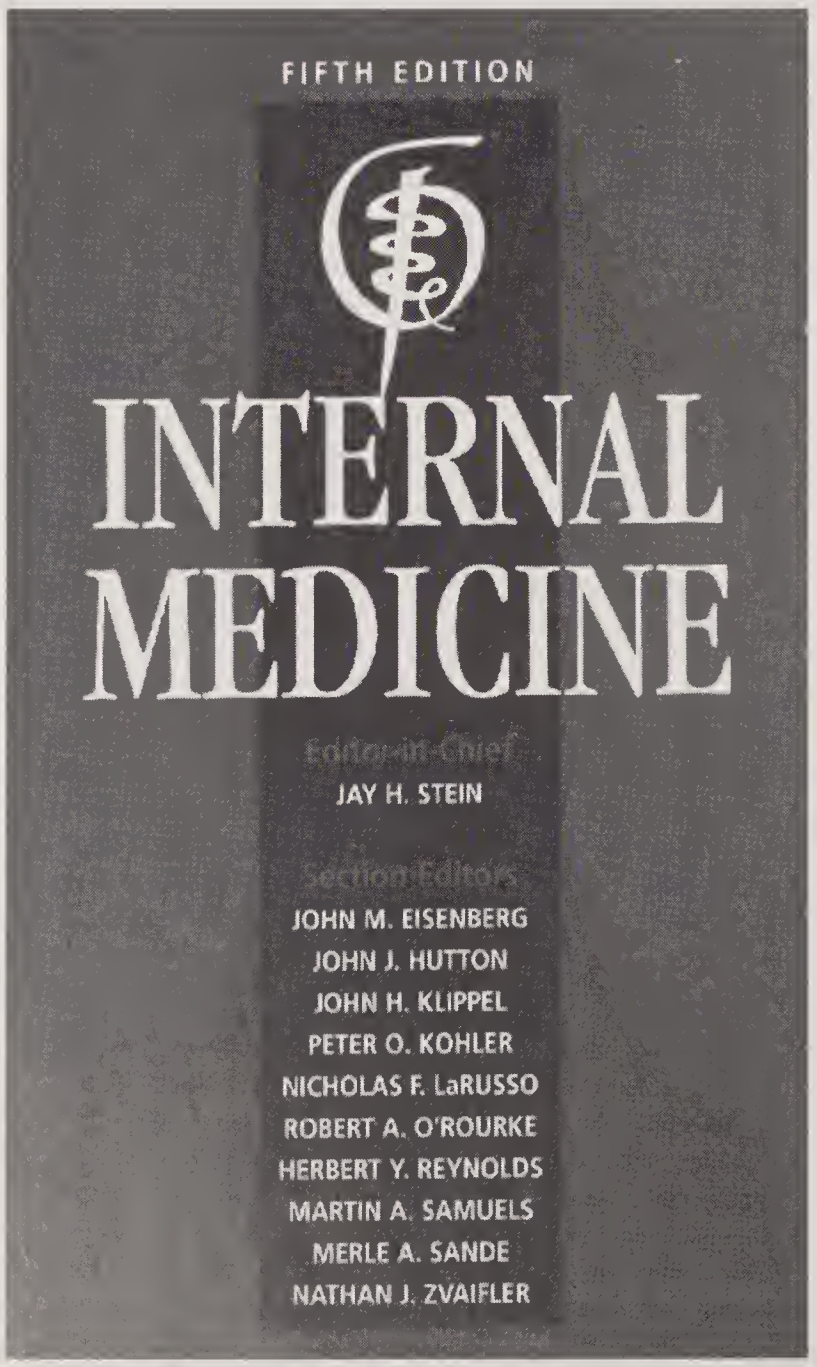
In short, *The Basic Science of Oncology* is an excellent primer into the cellular and molecular aspects of oncology and the fundamentals of cancer therapy. The text is geared toward undergraduate science and medical students in its content and presentation, and, as it is a paperback, toward their economic preferences as well. As such, the text can serve as an ideal resource for undergraduate students with an interest in oncology or cancer research, or as a needed supplement to introductory courses in oncology or cancer therapy.

Internal Medicine, Fifth Edition

Reviewed By Kevin Carter, MSc. (OT1)

Editor-in-Chief: Jay H. Stein
Publisher: Mosby Inc.
Date of Publication: 1998
Number of Pages: 2515

Overall Rating:	9/10
Strengths:	Well organized, illustrated and very comprehensive
Weaknesses:	Some sections too broad and do not follow the general format
Audience:	Medical students and practicing physicians



While internal medicine is a field which requires a great deal of lateral thinking and problem solving, at the core is a vast amount of basic medical knowledge that is seemingly overwhelming. For this reason, every medical student and physician requires a quick reference guide that can provide them with a wealth of knowledge at a glance. With internal medicine being such a broad topic, any editor that attempts the daunting task of creating a text with this much information in a well organized fashion is a brave soul indeed. In *The Fifth Edition of Internal Medicine*, Jay H. Stein and ten other section editors have succeeded in providing an excellent comprehensive medical encyclopedia and reference guide for both students and practicing physicians alike.

One of the keys to the success of this text is organization. The book is divided into ten parts by clinical subspecialty. These ten partitions are then subdivided into three sections; an introductory section, a section on lab tests and diagnostic methods, and a section on specific disease entities. The first chapter of the book is entitled "Introduction to Modern Medical Practice". This section covers topics ranging from the patient-physician encounter to statistics in diagnostic testing to clinical bioethics; all in only 34 pages. While each topic is really only touched upon, this section is truly one of the features that enable this text to stand apart from other similar books. The editors realize that all patient care cannot simply be ordered in a strict scientific format. Thus, this section reminds the medical student that medicine is as much of an art as a science.

Another strength of the text is that even with eleven editors and over two hundred contributors, the writing

remains at a consistently high level throughout. The reader doesn't feel like he or she is jumping from topic to topic but instead a flow is maintained. This simple feature assists the student tremendously in learning the topics at hand. The use of figures, tables and boxes is also helpful and appropriate throughout the text. A unique addition to the text are the "When to Refer" boxes. Located strategically throughout each section, these boxes aid both the student and the practicing physician in noting the key signs and symptoms of when to refer a patient to a specialist.

Although most sections of the text are organized into very similar formats, there are a few sections that differ slightly. For example, the section on neurologic disorders does not include a basic introduction before it delves into clinical and laboratory evaluations. For medical students this is an unfortunate feature, and overall, this distracts from the continuity of the entire text. Furthermore, the section on "Endocrine, Metabolism and Genetics" is too broad. With genetics being such an important part of modern medicine, it deserves consideration as its own specific section. Moreover, by grouping these three topics together, some clinical conditions are not explained in sufficient detail. The only other disadvantage of this book is its enormous size. While impressive looking, the text is large and cumbersome and could easily have been split into two volumes or placed on CD-ROM.

These features aside, *The Fifth Edition of Internal Medicine* is an essential text for both the medical student and the practicing physician. At over 2500 pages it is not a text to be read cover to cover but rather to be used as a quick reference. *Internal Medicine* covers a wide spectrum of topics and subspecialties, is easy to read, and is organized in such a fashion as to solidify the information in the mind of the reader. If purchased early in a medical student's career this reference is one which could easily be used throughout medical school.

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University of Toronto Medical Journal

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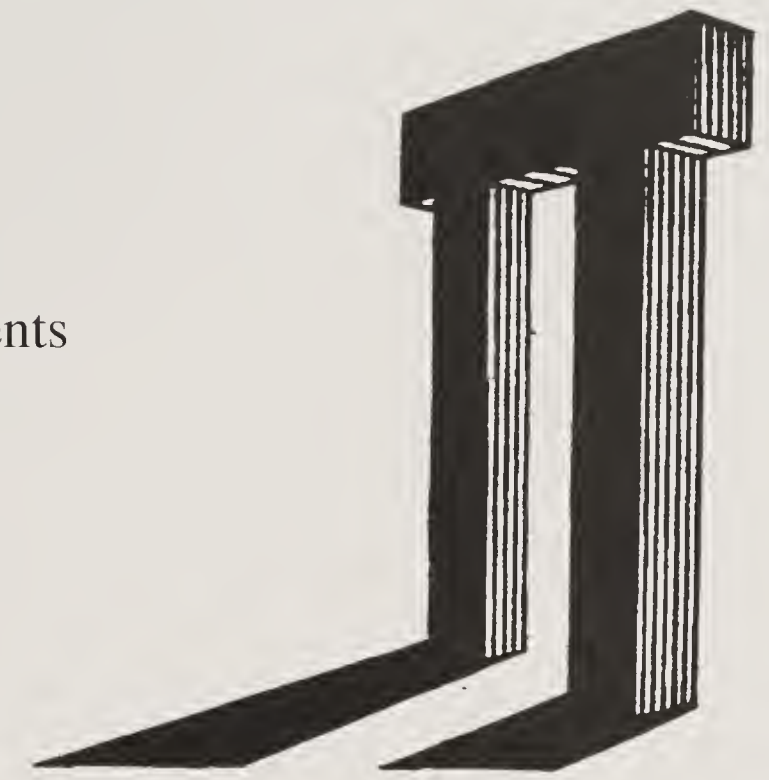

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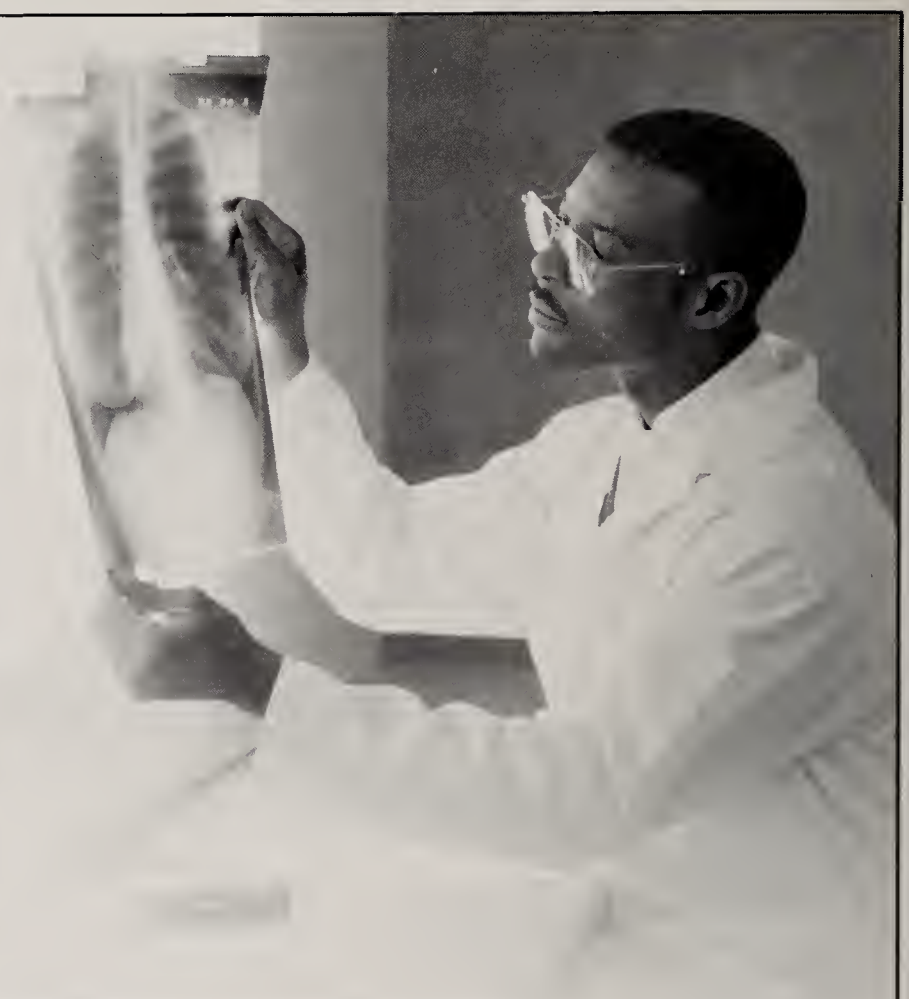

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